

International Society for Advancement of Cytometry (ISAC) Flow Cytometry Shared Resource Laboratory (SRL) Best Practices

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• Abstract

The purpose of this document is to define minimal standards for a flow cytometry shared resource laboratory (SRL) and provide guidance for best practices in several important areas. This effort is driven by the desire of International Society for the Advancement of Cytometry (ISAC) members in SRLs to define and maintain standards of excellence in flow cytometry, and act as a repository for key elements of this information (e.g. example SOPs/training material, etc.). These best practices are not intended to define specifically how to implement these recommendations, but rather to establish minimal goals for an SRL to address in order to achieve excellence. It is hoped that once these best practices are established and implemented they will serve as a template from which similar practices can be defined for other types of SRLs. Identification of the need for best practices first occurred through discussions at the CYTO 2013 SRL Forum, with the most important areas for which best practices should be defined identified through several surveys and SRL track workshops as part of CYTO 2014. © 2016 International Society for Advancement of Cytometry

• Key terms

flow cytometry shared resource; best practices; quality assurance; quality control; operations management; biosafety; data management; reproducibility in science; standard operating procedures; education and training

INTRODUCTION

THE term “Shared Resource Lab” has been adopted over the use of the term “Core Lab” to better define the role of shared instrumentation labs as a scientific partnership with researchers within an institution (1). Recently there has been a great deal of attention toward the lack of reproducibility in science and its financial impact (2–8). Shared Resource Laboratories (SRLs) have the responsibility and capability to ensure the generation of reproducible quality data. The SRL is unique in that it provides access to highly specialized technologies while serving as a technical and scientific resource that requires highly trained staff, professional facility management, proper financial oversight, and follows rigorous quality standards. The development of a comprehensive SRL Best Practices document is aimed at establishing a minimum set of standards that should be achievable by any SRL while providing the basic structure and guidelines to this end. The Best Practices initiative provides guidelines that SRLs can follow and implement in their facilities. There are multiple benefits to an SRL by implementing quality and operational standards within the lab. Establishing a best practices framework will lead to more effective SRLs that consistently produce quality data, provide exper-

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tise and high-level services, which ultimately will increase the probability of generating reproducible data.

It is envisioned that this document will be the first step in the creation of the ISAC Center of Excellence Recognition Program. The Center of Excellence Program will provide tangible acknowledgment for the SRL while establishing credibility for the investigators and the institution. These Best Practices will also serve as a resource for new or existing SRLs that want to achieve a level of excellence.

The long-term goal of these initiatives would be to generate a level of professionalism across SRLs that increases the overall quality and reproducibility of the research related to the field of flow cytometry.

In order to effectively represent the diversity of SRLs who provide flow cytometric services several initiatives were undertaken. Input was solicited from the entire SRL community through the use of two surveys; one to help understand the diversity, demographics, and career tracks represented within the SRL community, and another to better understand the issues, concerns, and current standards of practice of those working in SRLs. These surveys were distributed to all ISAC members that identified themselves as SRL staff and to SRL individuals outside of the ISAC membership through open solicitation on various list serves and social media. The results of the second survey were published on the ISAC website in 2014 (9) and served to provide a major source of content discussed during two CYTO 2014 workshops entitled: "Best Practices in the SRL" and "Career Development in the SRL." During the Best Practices Workshop small working groups began to discuss the minimal standards of practice in the top areas identified through the survey. Each small working group presented their discussions to all the workshop attendees for continued discussion and feedback. These discussions were documented by the workshop chairs and served as the basis from which a task force, composed of geographically diverse individuals from academia, industry, and biopharmaceutical SRLs, continued its efforts. What follows is the culmination of these discussions and efforts of the task force at addressing best practices for flow cytometry SRLs.

1. SOPs

Standard operating procedures (SOPs) are written management directives that describe routine and repetitive methods and processes sufficiently to ensure the integrity, quality,

consistency, reproducibility, and reconstruction of data or outcomes (2,6,8).

1.1. Why are SOPs Necessary?

SOPs help to ensure reliable reproducibility for repetitive processes (5). These reference documents provide a framework for organizational policies along with documentation of a variety of best practices from management issues to consistent laboratory practices (10–13). SOPs are especially essential for SRLs with multiple employees to ensure consistency across different procedures such as training, policies, QC, and biosafety.

1.2. Sections for a SOP (SOP for an SOP)

SOPs should maintain a similar structure so that they can be quickly identified by title, date of last revision, and purpose. This also improves efficiency when sharing with laboratory members, administrative staff, and/or collaborators (14–17). A recommendation for SOP format can be seen in Supporting Information Figure 1 and includes:

- Title page
- Revision number and date of revision
- Table of Contents
- Purpose
- Detailed description of procedure based on best practices
- Procedure monitoring
- Corrective actions
- Date of establishment and subsequent reviews (annually at a minimum)

1.3. Categories/Topics for SOPs Specific to SRLs

Each SRL should establish SOPs for routine procedures. Below are the recommended types of SOPs that an SRL should have in place.

1.3.1. Training and education. To ensure a quality and consistent education for self-operators, an SRL should have a SOP in place to ensure that each student receives the same training criteria (i.e. QC, data analysis, instrument operations, etc.). Benchmarks should be included to determine at what point a user can be identified as independent.

1.3.2. Maintenance. SRLs should establish a written SOP that outlines who (i.e. staff vs. user) is responsible for the maintenance of each type of instrument. This SOP should also entail how often (daily, weekly, monthly, etc.) the

maintenance should be performed and the details of this maintenance procedure.

1.3.3. Instrument QC. Instrument QC is critical to ensure quality data. SOPs should be in place that detail who (staff, user) and how often an instrument should be QC'd. It should also state the procedure used, calibration/standards material and the acceptable passing criteria.

1.3.4. Biosafety. Each SRL should establish a rigorous biosafety SOP. The Institutional Biosafety Committee should ideally approve this SOP. It should clearly state the level of biosafety (BSL1, BSL2, etc.) of the types of samples the laboratory can safely accept. It should also outline the types of personal protective equipment (PPE) worn, how to verify and validate aerosol containment, acceptable tolerances, and laser/chemical safety procedures. It should also detail the procedure used to decontaminate the instrument (see Biosafety section)

1.3.5. Lab policies and procedures. A written statement of laboratory policies and procedures is a must for any SRL. This document should entail rules of the laboratory, billing procedures, scheduling/cancellation policies, and disciplinary actions that may arise should abuse of the SRL policies take place. Ideally, this should be approved by the SRL's advisory committee and may even be posted on the facilities website so that everyone has clear access to this document, or alternatively, added to a user competency sign off document.

1.3.6. Emergency preparedness policies. Written SOPs should include procedures for instrument/electronics hardware shutdowns during power outages, floods, or potential national disaster. Policies should document the serial number for each instrument, as well as instrument location, proof of purchase, all instrument-related document locations, and emergency contact person and phone number in an event of a disaster. Other emergency preparedness policies should include institutional policies such as biohazard exposure plans (18).

1.3.7. Sample preparation guidelines and protocols (for SRLs that perform these functions). For flow cytometry

- Sort buffers/concentrations
- Filtering
- Collection vessel

1.3.8. Instrument setup/monitoring.

- Instrument startup
- Instrument settings
- Instrument validation
- Instrument monitoring during run
- Temperature stability

1.3.9. Data management.

- User responsibility

- SRL responsibility
- Back up procedures
- Data recovery

1.4. SOP Sharing

Using established SOPs as a template can save valuable time when setting up new procedures. It is also a good way to establish continuity between labs and institutions. When borrowing and utilizing established SOPs, one should modify it to one's specific needs taking into account any specific institutional, and/or industry, regulations/policies that may be different between institutions. To help foster collaborative sharing, the ISAC SRL Task Force is working toward establishing an ISAC host repository of SOPs from people willing and able to share.

1.5. SOPs in Industry

Flow cytometry resource labs in industry must comply with company specific policies regarding the format, content, and management of SOPs. Below are a few examples of SOPs that may be required, however, as each company may have specific rules regarding the use of SOPs, SRLs operating in industry should consult with the authorities within their company who oversee SOP development and distribution.

- Collaboration: Guidelines to ensure proper scientific disclosure and material transfer agreements should be in place prior to standard risk assessment practice performed by the company (policies vary).
- Public disclosure of information: Procedures for authorizing the exchange of company confidential information should be established. Approvals required
- Business purpose identified
- Legal requirements
- External party rights
- Data transfer and exchange: identify approved policies for use of electronic resources for external party information exchange.
- Approved file storage
- Internal document management
- Secure network storage
- Internal cloud services (accessible to collaborators)
- Unapproved file storage
- Non company approved devices
- Unauthorized cloud services (Google, Dropbox, Amazon Cloud, etc.)
- Company email
- Good laboratory practices (GLP)
- Company specific safety requirements

2. TRAINING AND EDUCATION

Educational SRL "best practices" covers a wide range of topics. Some education may take place within specific academic programs, but specifically within the SRL, a robust educational program is essential for quality assurance (6). Educational best practices should consist of both theory and

Education and Training



Figure 1. Educational SRL best practices cover a wide range of topics. The entirety of this information should be communicated to the SRL staff and where appropriate a subset of this information (encompassed by the inner circle) should be disseminated to the end user of the facility. [Color figure can be viewed at wileyonlinelibrary.com]

hands on training while being tailored to either staff or user, where appropriate (Figure 1) (1,19,20). All efforts of training and education for staff and facility users should be documented. Refer to the SOP section.

2.1. Instrumentation

As flow cytometry SRLs are likely to be technology and instrumentation centric, a large focus of the education within the lab should promote a thorough understanding of both the theoretical workings of the instrumentation as well as the specific details associated with running and acquiring samples on the instruments.

2.1.1. Education.

- General principles and theory of the technologies available in the lab, lab-specific instrumentation capabilities and configurations
- All laboratory safety policies and procedures (Biosafety, Chemical, Environmental, and Radiation (if applicable) Safety)

2.1.2. Training.

- Data Acquisition and storage
- QA/QC
- Daily–Weekly–Monthly maintenance
- Basic Troubleshooting
- Startup and Shutdown Procedures
- Cell Sorting specific instrumentation operation
 - Biosafety (Aerosol Management)
 - Sort setup checklist

- Sort monitoring
- Sterility
- Purity checks

2.2. Experimental Design

Note: Primarily a component of Education

Prior to data acquisition and in accordance with MIFlow-Cyt guidelines (21), a strong emphasis should be placed on the design and strategy of the assays that are needed. This will build an understanding of the specific instrumentation capabilities to ensure that the designed experiment is indeed feasible and that all the appropriate controls have been included.

- Controls—Instrument setup, gating and experimental
- Resources for reagents and protocols
- Sample Procurement
- Tissue dissociation, fixation, or permeabilization
- SOP's for basic sample staining
- Application specific Protocols
- Multiparametric panel design

2.3. Reagents

Note: Most SRLs only provide educational support in this area, but for those SRLs that have a wet lab, training in the proper use of reagents may also need to be established.

Understanding spectral properties of fluorescent dyes and choosing the appropriate cell preparation reagents are equally as important as the understanding of the instrumentation within an SRL. Educational resources regarding these topics should be readily available for users.

- Fluorescence
- Spectral viewers
- Cell Cycle and proliferation dyes
- Antibody basics
- Functional dyes
 - Apoptosis
 - Membrane potential
 - Viability dyes
- Fixation and permeabilization buffers
- RBC lysis
- Potential assay reagent interactions (dye-dye interactions, heavy metals and quantum dots, Annexin V binding and certain buffers, etc.)

2.4. Lab Safety

Laboratory safety (refer to Laboratory Safety section for more detailed outline) is essential in an SRL to protect staff and users from a variety of hazards in a core lab. Since many individuals will visit an SRL day to day and may not be directly supervised when using the lab, safety training should include comprehensive sections on the potential hazards as well as procedures in the event of an incident.

- Biosafety
- Chemical
- Laser
- Emergency response
- Electrical

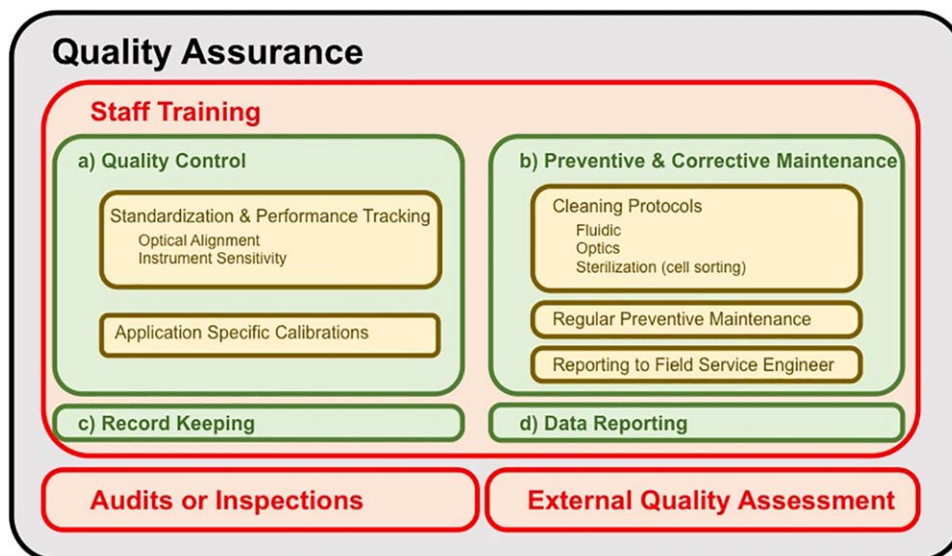


Figure 2. Quality assurance in the SRL requires the development of a multilayered set of thoughtful procedures that encompass staff training and execution of (a) quality control activities, such as instrument standardization & performance tracking and application-specific calibrations; (b) preventive and corrective maintenance, such as instrument-specific cleaning and troubleshooting SOPs; (c) record keeping; and (d) data reporting. In addition, implementing audits or external inspections and setting up an external Quality Assessment Program will enhance the QA program and consequently the overall quality of the SRL.

2.5. Data Analysis

A comprehensive understanding of data analysis incorporates many disciplines including instrumentation, statistics, biology, and photonics. Training and education best practices for data analysis should give the essential background on these disciplines along with providing the hands on training with the appropriate software.

- General analysis theory including gating logic
- Specific software training
- Data presentation
- Statistics
- Specialized modeling tools
- Publication guidelines/MIFlowCyt

It should be noted that a robust standard for the minimum information about a flow cytometry experiment, MIFlowCyt, has previously been published (21). Awareness and adherence should be the goal for publications and should be highlighted during educational curricula.

2.6. Facility Policies

Upon initial introduction to the SRL, all users should be made aware of resources available to them as well the facility policies. Staff of the SRL should take necessary measures to insure users have been made aware of and understand the facility's policies. This will help acclimate new users and provide necessary information for addressing problematic situations when they arise within the SRL.

- Facility website
- Scheduling website and policies

- After hours usage
- Billing procedures and rates
- Cancellation and late arrival policies
- Customer service
- Facility acknowledgement for publications
- Overview of educational program
- Policies for reporting instrumentation problems

2.7. Continuing Education

The field of flow cytometry is quickly evolving and growing. This growth takes place within the technological aspects as well as in reagents and assays. It is essential for SRL staff to be current in the new advancements in order to advise and assist SRL clients. Below is a list of potential useful opportunities for continued education within the SRL. These activities could be at the provider or attendance level. For example, invitations to present seminars, webinars, workshops, etc. are also considered beneficial to staff in terms of continuing education. The following represent some examples of opportunities for continuing education:

- Cytometry Certification-ICCE (www.cytometrycertification.org)
- Conferences (list of user groups/ABRF/CYTO etc.)
- Webinars
- Research in Progress seminars
- Instrument manufacturer training
- Journal clubs
- Independent research

3. QUALITY ASSURANCE

Adequate quality assurance (QA) practices within SRLs are critical to the overall function of such facilities (1).

Preventive and corrective maintenance, calibration and tracking of instrument performance requires a reasonable set of “best practices” to ensure that data of high quality is generated and reproducible within the SRL as well as in external labs (2,4,6,8). SRLs must also have in place a set of systematic procedures to ensure that quality is implemented correctly in the lab (1). SRLs will have SOPs for instrument quality control (QC), but also for preventive and corrective action, personnel training of QC procedures, record keeping and reporting QC data (Figure 2). The best practices presented here represent what should be minimally present to ensure individual SRLs develop SOPs that meet these criteria.

3.1. Instrument Quality Control

Data quality and reproducibility are directly related to instrument performance. Adequate instrument quality control procedures must be performed routinely to ensure best instrument performance, which typically consist of running QC particles for which acceptable metrics have been determined for each instrument. In addition, specific or specialized applications may require a particular set of calibration procedures that should be performed and documented prior to running the experiments. Instrument QC SOPs must exist (see SOP section) and should include daily/regular record of instrument performance metrics.

3.1.1. Standardization and performance tracking. Instrument standardization and regular performance tracking are essential to provide investigators with reliable data (22). Optical alignment and detection sensitivity are two key performance metrics that must be evaluated on a regular basis.

3.1.1.1. Optical alignment. Optical alignment is assessed using standard or “reference” particles, as defined by the user, laboratory, or other acknowledged authority. This particle generally has a low intrinsic CV and monitors core focusing and laser alignment (22–25). The following are recommendations for assessing and tracking optical alignment:

- Assessment of optical alignment is performed daily, or at least on days instrument is used
- Performance criteria are clearly defined
- Establish acceptable reference ranges (MFI, SD, and CV)
- Performance is charted and monitored, and made available to every user
- Records kept for standards and component changes according to governing policies
- Corrective action performed if criteria are not met
- Troubleshooting SOPs are defined

3.1.1.2. Instrument sensitivity. Instrument sensitivity is a critical assessment for dim sample detection and should be integrated into quality assurance protocols. Sensitivity is assessed using a calibrator/standard with clearly defined properties that assign a metric (e.g. MESF) to instrument performance or multiplex beads with blank, dim, and bright bead

populations (26). The following are recommendations for maintaining sensitivity:

- Sensitivity (e.g., Q, B, and Resolution limit (26) or laser output and pinhole alignment, is performed regularly (monthly at a minimum), and especially after an instrument has undergone any repairs or maintenance (22))
- Performance criteria are clearly defined
- Performance is charted and monitored, and made available to users
- Records kept for calibration sample and component changes according to governing policies
- QA: Corrective action performed if criteria are not met
- Troubleshooting SOPs are defined

3.1.2. Application-specific calibration. There are specific applications requiring calibration beyond alignment and sensitivity and best practice warrants a calibration assessment immediately prior to experimentation. These applications include, but are not limited to: spectral overlap compensation in multicolor immunophenotyping, drop-charge delay calibration for cell sorting, xyz alignment for multiple laser wavelengths, linearity checks for DNA Ploidy and fluorescence calibration (MESF) for small particle analyses. Best practice SRLs will establish SOPs for applications requiring specific calibration. Following is the recommended frequency, at the minimum, for calibrations:

- Calibration is performed at least on days the assay is performed, or just before starting the experiment
- All calibrations performed must be documented

3.2. Preventive and Corrective Maintenance

SRLs should have SOPs for regular maintenance and troubleshooting. These should include:

- Postexperiment cleaning protocols
- Daily cleaning protocols
- Monthly cleaning protocols
- Semiannual preventative maintenance (including filter replacements)
- Optic cleaning
- Flow cell cleaning
- For cell sorters—instrument sterilization (and sterility testing)
- Criteria for requesting intervention of a Field Service Engineer

Depending on several factors, including financial conditions, instrument type, number, and usage, SRL may seek service contracts for preventive and corrective maintenance but would be required to keep records of all service visits and corrective actions. Instrument QC should be performed by the SRL staff immediately after instrument has been serviced (see Instrument Quality Control section).

3.3. Staff Training

The implementation of QA begins with training. SRLs should determine what degree of training SRL personnel and users is sufficient for achieving QA in the flow cytometry SRL. Given the fast pace at which the technologies evolve, staff should participate in regular and continued professional development programs. SRL staff should be trained in basic troubleshooting techniques to identify the source of problems (see Training and Education section).

3.4. Record Keeping and Data Reporting

All instrument performance evaluations and maintenance interventions must be adequately recorded and it should be easy to track performance over time. Providing this information to all users of the instruments will allow better QA. There should also be mechanisms in place so that it is possible to retrieve any results that may have been affected by unacceptable performance discovered through the QA procedures. To this end, it is recommended that SRLs maintain, and make available to users, a historical detail of instrument upgrades and replacements of parts affecting fluorescence output and fluorescence collection, as defined by MiFlowCyt recommendations (21). For example, an instrument detail would include:

- Manufacturer
- Instrument model
- Configuration and settings
 - Flow cell type
 - Other relevant flow cell and fluidic information
 - Light source(s)
- Excitation optics configuration
 - Optic filters including install date, manufacturer, model type
- Optical detectors
- Detector voltage and/or gains

Quality assurance is fundamental for experimental reproducibility. SRLs should go to every extent to encourage researchers to follow MiFlowCyt guidelines (21) from data acquisition to data reporting.

3.5. Audits or Inspections

Inspections or audits can greatly increase the working quality of SRLs. Internal (by institutional personnel) or external inspections (by other SRL leaders from other institutions, for example) should ideally occur on a yearly basis. Results of inspections/audits should be well documented with any findings, outcomes and actions recorded with subsequent follow-up.

3.6. External Quality Assessment

Having SRLs participate in external proficiency exercises (if existent) that allow direct comparisons of sample results with other laboratories will help identify any quality issues.

4. LABORATORY SAFETY

The importance of adequate safety practices within the SRL is critical to the overall function of such facilities. Working in a “shared” environment in which a large variety of

biological samples are introduced requires a reasonable set of ‘best practices’ to ensure the safety of all individuals who access the shared facility (27–30). The best practices presented here represent what should be minimally present to provide a safe working environment. Individual SRLs should develop specific SOPs that meet these criteria and are in compliance with local and national biosafety regulations.

4.1. Training

One of the most critical activities to ensure a safe work environment is to make certain those that share that environment are educated/trained about the potential risks and hazards and how to appropriately manage them to minimize risk (27). This activity should be developed for both the users (customers) of the facility as well as the staff of the facility. An adequate training program should include:

- Familiarization with local and national laboratory safety regulations
- Familiarity with individual sample requirements that require special handling (30)
- Easily accessible laboratory biosafety manual that documents the SRLs SOPs for minimizing risk of exposure and handling of breaches in containment; including documentation and monitoring of engineering controls (e.g. biosafety cabinets)
- Annual review of SOPs and revisions as necessary
- Documentation of staff and user training annually
- Methods for monitoring compliance with SRL biosafety SOPs

4.2. Risk Assessment

In order to have an effective biosafety plan an SRL must have mechanisms in place to know and evaluate the potential biosafety risks (29,30). The following are recommended practices for accomplishing this:

- Mechanism for assessing risk of each user’s protocols/samples that will be performed in SRL
- Establishment of a communication process with institutional biosafety officials to properly evaluate/confirm risk
- Knowledge of or access to published biosafety risk level definitions/requirements from appropriate regulatory bodies
- List of approved biomaterials which can be accepted by the SRL
- List of biomaterials which will NOT be accepted by the SRL
- Written approvals for each individual experimental condition which are instrument, sample, and person specific

4.3. Exposure Plan

SRLs often deal with biological specimens that have a variety of potential biohazardous risks. SRLs have the responsibility of establishing a plan that will minimize exposure of users and staff to these risks as best as is reasonably possible (29,30). The following practices, at a minimum, should be included in an SRLs exposure plan:

- SOPs for dealing with spills/accidents involving biohazardous materials

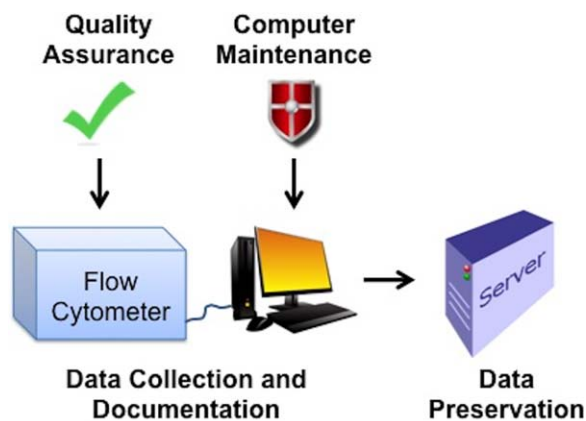


Figure 3. Central to the data management workflow is data collection from a flow cytometer. During data collection, a user should document any relevant information to describe the dataset that will make it identifiable, easy to locate and analyze. Quality assurance information should be gathered to ensure data is of good integrity. Data should be stored in a way that promotes long-term preservation. Computers that collect data from the instruments should be properly maintained to minimize data corruption and loss. [Color figure can be viewed at wileyonlinelibrary.com]

- Procedures for managing and containing aerosols in a way which maximally reduces instrument operators/users' exposure, including SOPs for evaluating effectiveness of procedures, testing frequency, documentation of results and corrective actions (31)
- SOPs for minimizing instrument clogging
- SOPs for waste management
- SOPs for instrumentation and lab area cleanup and decontamination
- SOPs for the use of PPE, i.e. which and under what circumstance
- SOPs for cleaning/decontamination of instrument prior to maintenance
- SOPs for biohazardous waste management

4.4. Physical Environment

The appointment of space for an SRL must be consistent with a reasonable ability to conduct work in a safe manner (1,30). The space should include at a minimum:

- Availability of hand and eye washing stations
- Provision of basic PPE, i.e. gloves, lab coats, respirators (if applicable, face shields/masks (if applicable))
- Controlled/secured space for minimizing entrance by unqualified/untrained personnel
- Availability of Biosafety Cabinets (BSCs) or other appropriate devices to contain/manage aerosols where applicable (32)
- Reasonable square footage, HVAC (i.e. properly balanced airflow) and power consistent with safe laboratory practices and minimization of accidents and maximization of safety
- Display of appropriate safety signage where required (e.g. Laser in Operation, Warning: Biohazardous Materials in Use)

4.5. Other Administrative Lab Safety Best Practices

In addition to the above it is also important that the following best practices are in place (27):

- Laboratory Management at all levels support and enforce the SRLs Biosafety Plan
- Institutional management are actively involved with and support the SRLs Biosafety Plan, particularly the institutional biosafety officers
- Management of the SRL are engaged with the biosafety community at ISAC and provide suggestions and feedback as appropriate
- All other laboratory safety SOPs and practices are in place in accordance with institutional policies; i.e. chemical, laser, radiation safety, etc.
- Procedures are in place to insure the safety of all outside engineers/contractors, including disclosure of potential hazards and training on how to deal with such hazards.

5. DATA MANAGEMENT

Data management is critical to long term identification and preservation of experimental observations made in an SRL (3–5,8). Best practices should include guidelines on collection, quality assurance, description and preservation of data files and computer maintenance for flow cytometry systems (33,34). Figure 3 summarizes each of these processes and how they are related in the workflow of data management. While institutions may vary on methods of and resources for data management, this section highlights essential procedures to be conducted in flow cytometry SRLs. For SRLs within industry and patient care facilities, company specific policies may require additional measures to ensure data confidentiality. In addition, many funding and governmental agencies require investigators to adhere to guidelines to promote responsible data management and sharing (35–38). These best practices will support investigators efforts to ensure adherence to data access and data management policies.

5.1. Data Collection

Data collection is the process by which the user or SRL staff member generates results from sample analysis and how these results are organized and recorded. In accordance with MIFlowCyt guidelines (21), the SRL should:

- Provide guidelines on what parameters to collect and proper annotation to enable accurate interpretation of results
- Provide guidelines to produce statistically meaningful data sets (e.g. number of events to record)
- Provide direction on file format to save for proper data analysis
- Establish and inform whose responsibility it is to export/save the data (SRL staff or user)
- Provide information on file size limits for each system

5.2. Data Documentation/Description

Data documentation is essential for long-term understanding of experimental parameters so that data is easy to locate, analyze, and reuse. The SRL should:

- Provide direction on producing self-describing data sets by defining metadata and file names using standard terminology (21,39,40)
- Provide information on and encourage adherence to publication standards (e.g. information to include in materials and methods, etc. (21))
- Encourage that data files used for publication are deposited in the appropriate repositories when applicable (e.g. FCS Data Repository found at <https://flowrepository.org>)
- When appropriate, de-identify data by encoding sensitive sample information (41)

5.3. Quality Assurance

Quality assurance allows the identification of erroneous data sets and promotes correct interpretation of experimental results. The SRL should:

- Have in place an instrument QA plan (see Instrument Quality Assurance section)
- Define methods to ensure data collection was problem-free. For example, using the time parameter in the FCS file or the inclusion of standard particles (e.g. beads), and/or other automated methods (e.g. FlowClean, flowAI) (42,43)
 - Provide QC results to users as needed to ensure good instrument operation during data acquisition
- Identify and communicate data sets that are erroneous.

5.4. Data Preservation

Data preservation involves the process of transferring data to a long-term, secure archive to retain a copy of and prevent unauthorized access to data files (33,44). There can be differences in institutional guidelines for data preservation and storage; an example of this can be found in Table 1.

- Some combination of short-term and long-term storage should be provided to SRL staff or users to immediately preserve data and allow for restoration of data files in case of corruption.
 - Methods to achieve this can range from manual transfer to external hard drives, to software assisted backup to institutional server via Ethernet network. The specific method used for data file transfer and archiving is dependent on institutional policies and resources that are available to the SRL.
 - Archives ideally are kept off site so data is retrievable if facilities are destroyed.
- Instruction should be provided on standard method of data transfer from the instrument to storage that minimizes introduction of data corruption. For example:
 - Minimize the introduction of computer viruses by prohibiting the use of flash drives.

Table 1. Examples and suggested frequencies of tasks that might be performed by a shared resource facility when adhering to data management best practices

DATA MANAGEMENT TASK	SUGGESTED FREQUENCIES ^a
Recording data with appropriate controls and metadata saved in FCS files	When collecting data
Exporting of data	After collecting data
Back up of data	After collecting data/wk
Data management on instruments/computers	Weekly
Antiviral software updates	Monthly
Computer system maintenance e.g., Defrag computer	Weekly or monthly
Move data to long-term storage	After 1 yr
Deletion of data	After 10 yr

^a These frequencies may vary according to funding and institutional guidelines. Where discrepancies exist, the longer period should always be used.

- Generation of initial checksums that can be used to verify integrity of data at all subsequent stages.
- Provide clear information to users on length of time data is stored in each entity (computer, short-term and long-term storage) by SRL/institution. Requirements will be dependent on several factors such as institution, funding agency, country etc.

5.5. Computer Usage and Maintenance

Virtually all SRL technologies operate using some form of computer. The maintenance of the instrument computer is essential to problem-free data generation and minimizes data corruption and data loss (33).

- Whenever possible, individual or investigator specific login credentials should be used to promote data security.
- SRL staff should perform some form of regular data management on instrument computers to maintain optimal operation. For example:
 - Remove old data and/or templates when appropriate to keep enough free hard drive space for the operating system to run efficiently.
- Perform regular computer maintenance as recommended by institutional IT department. For example:
 - Install antiviral software as recommended by institution and keep current.
 - Keep current on operating system updates unless updates are known to interfere with instrument operation.
 - Run system maintenance such as hard drive defragmentation, and disk cleanup.
 - Remove unwanted/unused applications or programs.

6. STAFFING

Staffing levels are not simply about how many staff an SRL has per instrument or even the number of staff per

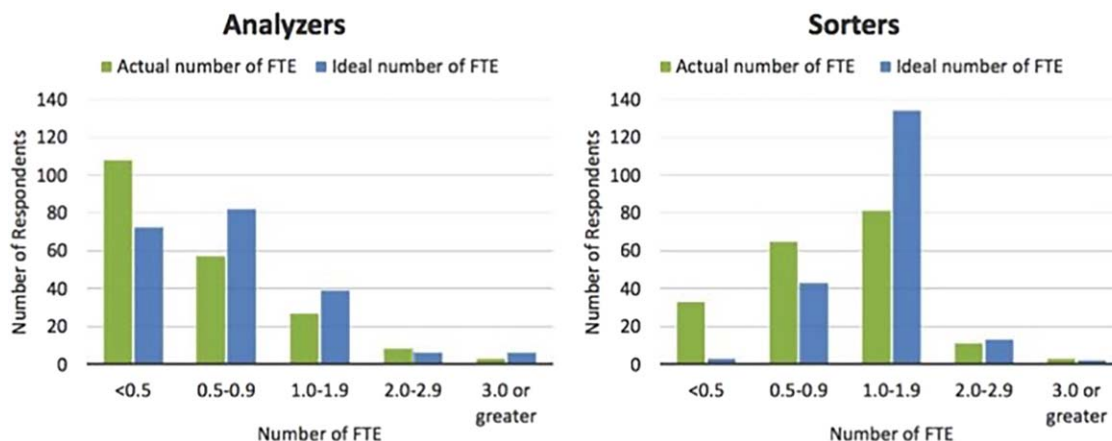


Figure 4. Data from ISACs 2014 Survey on SRL career tracks and best practices (9). Answers from 209 respondents to the questions of their SRLs current staffing level per instrument type as well as their “ideal” staffing level. While each SRL has different needs and goals, contributing to the variance in responses, there is a clear trend in the data. Approximately 70% of respondents believe analytical cytometers require less than one FTE, while cell sorters are each believed to require at least one FTE. Of 235 respondents to the survey that indicated a role in an SRL, 49% were managers, 23% directors, and 17% staff. [Color figure can be viewed at wileyonlinelibrary.com]

instrument class. Obtaining and maintaining the correct staffing levels in a technologically dynamic environment involves matching the staffing level, expertise and capabilities to the strategic goals of the facility. This process will require ongoing staff training and fine tuning (45). Maximizing the effectiveness of SRL staff is often a difficult and complex process, one that may be assisted through the following process:

6.1. Define Expectations for Staff Performance

6.1.1. Set goals of the facility. The setting of overall goals for the facility will better position the SRL to determine what type and how many staff members are required. For example, a facility that has a goal of developing new methods, instruments, approaches, i.e. adding value through the advancement of cytometry, will generally require more staff than a lab processing the same amount of work without the focus on development.

6.1.2. Set goals of the individual. Once one knows the types of people required to meet the overall SRL goals and the individual team/project goals, one can then match existing people to the given role and, if required, hire individuals with the required skill set to compliment the team. While it may be tempting to hire only technically gifted individuals, flow cytometry SRLs require more than just technical sophistication to survive and flourish.

6.2. Determine Staffing Levels

The 2013 ISAC SRL Survey (9) can be used as a good reference point for determining the number of staff needed in an SRL as seen in Figure 4. However, actual numbers should be determined by evaluating the specific needs of the users of the facility and by taking into consideration many of the smaller, often overlooked, tasks that take up much of the staff’s time.

A flow cytometry SRL should consider the nature of the work being carried out and the services offered (46). For example, when determining the number of sorter operators required it is important to know:

- Will the operator be continuously engaged in the sort process (as might happen when many samples are run per sort as opposed to a single tube long sort)?
- Is user operated sorting allowed?
- Are the hours of sorting amenable to a single operator? (e.g., long sorts may require multiple operators, especially in hazardous environments).

The ramifications of being understaffed are obvious, however, overstaffing can also be problematic from a cost-efficiency perspective and the impact on rate setting, if applicable. The following assessment will help to make appropriate decisions regarding how many staff members are needed:

- How many pieces of equipment are in the SRL?
- How complex is the equipment?
- Are the staffing ratios substantially outside of the industry norm?
 - If so why?
- How knowledgeable/experienced is the user base?
- Does staff have significant other commitments other than being operators?
- How accessible are assisted services, i.e., wait times for an appointment?
- How many users need to be supported and trained in any given year?

6.3. Determine the Skill Sets Required

This will most likely have been achieved during the goal setting exercise above, however, as with all aspects of cytometry, this is an iterative process and can always be refined. It should also be revisited at least once per year for every staff member—preferably with the individual staff member’s input to ensure skill levels are maintained.

Some useful questions to ask may include:

- Does staff need to be able to provide advice?
 - Is this advice technical, biological or both?

- Will the staff be expected to develop their own projects?
- How complex are the SRLs systems (both equipment and laboratory)?
- Is certification required?
- Customer service/focus
- Do we outsource some of the responsibilities?
 - Service contracts with manufacturers
 - What level of assistance is available from the IT department?
 - Will management or staff need to market the SRL services?
 - What are the financial and administrative tasks required?

6.4. Clearly Define the Task Expected of the Staff

The level to which this is done will be dependent on each individual staff member, some may respond to a highly structured workplace, others less so. Encouragement and adequate recognition of staff achievements requires some form of expectation defined at the beginning.

Tasks should be defined in the **SMART** format (47,48):

- Specific
- Measurable
- Attainable & Agreed upon by all
- Relevant & Realistic
- Time bound

6.5. Recruitment/Retention: Understand that Good Staff will Leave

A good SRL will produce not only users that go on to utilize flow cytometric techniques to advance science but also staff members that move on to help spread the skills they have developed. Good staff, however, may eventually leave and this brings with it challenges. It should be remembered that losing a good staff member is always better than retaining a bad one.

Listening, supporting, and providing development opportunities is one way to ensure that staff in the SRL are happy, productive, and committed.

If staff does leave, be prepared to replace them in a timely manner so as not to induce service shortages. The disruption caused by the unexpected loss of staff can be minimized if the following mechanisms are already in place:

- Position description—any changes should be done at the beginning of the recruitment process
- Approval to recruit for the vacancy
- Budgetary considerations for salary
- Recruitment plan developed through institutional Human Resources

7. OPERATIONS

One of the most important aspects of a well-run SRL is the operational structure of the facility. A properly managed SRL involves best practices that provide necessary oversight, strategic and fiscal management/planning, self-assessments, and external reviews for evaluating the facility's performance (1,49). The following areas should be addressed:

7.1. Management

- SRL should have a qualified manager and/or director whose roles and reporting structure are clearly defined (1).
- Individuals in management roles are given reasonable authority to make short- and long-term decisions to insure the efficiency and effectiveness of the SRL.

7.2. SRL Oversight (Advisory Board)

To insure the proper management and function of an SRL, oversight by a committee or advisory board is recommended. These boards or committees are generally composed of individuals who have a vested interest in the proper operation of the SRL (1).

- Composition
 - Prominent users of the facility
 - Individuals who have budgetary authority
 - Individuals with institutional influence
 - All members are clear of conflict of interest
- Frequency of meetings
 - No less than twice per year
- Defined roles/term length of members
- Minutes of all meetings should be recorded

7.3. SRL Performance Assessment (Internal and External)

Continual Process Improvement (CPI) is a necessary component of an effective SRL. In order for this process to take place, an SRL needs timely and accurate data from which to evaluate performance and identify areas for improvement (49). The following mechanisms are useful tools for this purpose.

- Internal client surveys
- External client surveys
- External core review
- Benchmarking

7.4. Annual Reports/Business Plans

It is important for an SRL to prepare an annual review and report of the facility's operation (1,49). Both successes and challenges should be reported. The following additional information should be included:

- Services/equipment changes (additions/deletions)
- Staff changes
- Strength, Weakness, Opportunity and Threat (SWOT) analyses (50)
- Usage information
- Budget and justification
- Major accomplishments
- Future milestones

7.5. Annual Budget Development with Quarterly Review

Preparation and periodic review of an annual operational budget is critical to the proper management of an SRL (1). This process is important for understanding the fiscal history

of the facility, as well as planning for the future. The importance of accurate historical data cannot be overstated. This is also a good time to think about upcoming changes that may impact your budget; i.e., addition of new staff or contractual salary increases, instrumentation coming off warranty, implementation, or deletion of services, new sources of revenue or potential losses of revenue, etc. Annual budgets are often prepared in coordination with annual reports or business plans. Most important is the regular review, quarterly at a minimum, of projected versus actuals so corrective actions can be taken as necessary. Reasonable budgets include:

- Revenues
 - Chargebacks
 - Grant support
 - Institutional subsidy
 - Other revenue sources
- Expenditures
 - Personnel costs (including benefits)
 - Other than personnel
 - Supplies
 - Reagents
 - Equipment maintenance
 - Travel/education (if permitted)
 - Miscellaneous

If budgets are prepared at a level separate from the SRL, the SRL manager should have an opportunity for input during the development and have access to periodic review of the budget for assessing the SRL's fiscal performance.

7.6. Facility Use Policies and Procedures

All facility use policies and procedures need to be clearly communicated in an easily accessible format. Care must be exercised when establishing policies and procedures to insure they are fair and reasonable and do not violate any institutional or governmental regulations/policies (51). Policies and procedures should be reviewed and approved by an Advisory Board/Committee.

7.7. Facility Communications

Communication is essential for ensuring all parties have access to information necessary for the delivery or usage of services in the SRL.

- Website
- Policies and procedures
- Rates
- Informational resources
- Instructions for using facility
- Contact information for facility staff/management
- Newsletter or other periodic communication of changes
- Email
- Social Media (52)

8. SUMMARY

SRLs have become major providers of services and technology in the flow cytometry field. While the responsibility of

publishing accurate reproducible data ultimately lies with the investigator, the role of SRLs in this process is a critical one. These Shared Resource Laboratory Best Practices were established to provide the basis for a standardized level of operation for ensuring data produced in flow cytometry SRLs is reproducible and of high quality. These guidelines encompass minimal goals for SOP creation, quality assurance, education, biosafety, data management, staffing, and general operations within SRLs, which will allow for more consistent and effective approaches to SRL operations. It is hoped that once these Best Practices are established and implemented, with minor modifications, they can serve as a template from which similar practices can be defined for other types of SRLs.

These SRL Best Practices can serve as the basis for criteria for any future ISAC SRL recognition program. Encouragement of SRLs to adhere to the above Best Practices ensure that those recognized will offer the higher level of service and expertise the ISAC Shared Resource Laboratories Task Force aims to advance.

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APPENDIX

ADDITIONAL RESOURCES

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