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James H. Nichols, PhD, DABCC, FACB, has volunteered for CLSI as:
- Chairholder of the EP23™ document development committee
- Chairholder of the Point-of-Care Testing (POCT) consensus committee
- Member of the Evaluation Protocols consensus committee

He has no commercial relationships to disclose with respect to this program.
Objectives

• Review key aspects of risk management.

• Recognize common error sources in the laboratory.

• Develop a quality control plan (QCP) for a simple CLIA* moderate complexity device.

* CLIA, Clinical Laboratory Improvement Amendments.
Risk

Would you walk underneath this piano?
Risk Management

• Clinical laboratories conduct a number of activities that could be considered risk management:
  – Evaluating the performance of new devices
  – Troubleshooting instrument problems (failed QC)
  – Responding to physician complaints (POCT does not match laboratory)
  – Estimating harm to a patient from incorrect results
  – Taking actions to prevent errors (training, QC lockout)
• So, risk management is not a new concept to the laboratory, just a formal term for what we are already doing every day.
Risk Management Definition

• Systematic application of management policies, procedures, and practices to the tasks of analyzing, evaluating, controlling, and monitoring risk (ISO 14971*)

Risk Definition

• Risk – the chance of suffering or encountering harm or loss (*Webster's Dictionary and Thesaurus*. Ashland, Ohio: Landoll; 1993.)
• Risk can be estimated through a combination of the probability of occurrence of harm and the severity of that harm (*ISO/IEC Guide 51*).
• Risk, essentially, is the potential for an error to occur.

There is no “perfect” POCT device, otherwise we would all be using it!

Tricorder App
No device is foolproof…
for a sufficiently talented fool!

(attributed to Dr. Carol Rauch, a distinguished colleague)
What Could Go Wrong?
Sources of Laboratory Error

• **Environmental:**
  – Temperature
  – Humidity
  – Light intensity
  – Altitude

• **Operator:**
  – Improper specimen preparation, handling
  – Incorrect test interpretation
  – Failure to follow test system instructions

• **Specimen:**
  – Bubbles
  – Clots
  – Incorrect tube additive

• **Analysis:**
  – Calibration factor incorrect
  – Mechanical failure
Managing Risk With a Control Process

- Once we identify the risks, we need to detect and prevent those errors from harming the patient.
- Control processes reduce risk by enhancing the detection of errors or limiting harm if errors go undetected.
- Control processes can take many forms, from liquid QC to engineered checks within a device.
Managing Risk With a Quality Control Process
Historical Quality Control

• QC was historically used to document stability of an analytical system (environment, operator, and analyzer).
• The 1950s industrial model of quality in an analytical process involved analyzing a surrogate sample like a patient sample. This “control” contained a known amount of measured analyte.
• If the analytical system can achieve the desired result using the control, then the system is stable and quality products (the patient results) are being produced.
Quality Control and Systematic Errors

- Systematic errors affect every test in a constant and predictable manner.
- Errors can occur from one point forward, or for a limited period of time.
- QC samples do a good job at detecting systematic errors:
  - Reagent deterioration or preparation
  - Improper storage or shipment conditions
  - Incorrect operator technique (e.g., dilution, pipette setting)
  - Calibration errors (e.g., wrong setpoint, factors)
Quality Control and Random Errors

- Errors that affect individual samples in a random and unpredictable fashion:
  - Clots
  - Bubbles
  - Interfering substances
- QC samples do a poor job at detecting random errors unless the error specifically occurred with the QC sample.
Quality Control

• A stabilized surrogate sample of known concentration that is analyzed like a patient sample to determine assay recovery and result stability over time

• Advantages
  – QC has target values: if the assay recovers the target, then everything is assumed stable (ie, instrument, reagent, operator, sample).
  – QC monitors the end product (result) of the entire test system.

• Disadvantages
  – Patients’ results can be reported before problem is detected.
  – When problem is detected, one must go back and reanalyze patients’ results since the last “good” QC.

• Need to get to fully automated analyzers that eliminate errors up front, and provide assured quality with every sample
  – Until that time, a robust QCP is needed.
Types of Quality Control

- “On-Board” or Analyzer QC – built-in device controls or system checks
- Internal QC – laboratory-analyzed surrogate sample controls
- External QC – blind proficiency survey; samples sent a few times a year to grade an individual laboratory’s performance against other laboratories
- Other types of QC – control processes either engineered by a manufacturer or enacted by a laboratory to ensure reliable results (eg, checking the temperature in a shipping container of new reagents)
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Quality Control Processes

• For some devices, QC procedures can be an essential risk control measure.
• Depending on the design of the device, these QC procedures can help users ensure the quality of results by:
  – Verifying the suitability of analytical systems (eg, sample, reagents, instruments, and/or users)
  – Monitoring the precision and trueness of measurement results
  – Preventing false-negative and false-positive results
  – Identifying fault conditions that could lead to inaccurate results
  – Troubleshooting problems that require corrective action

Quality Control

• No single QC procedure can cover all devices, because devices may differ in design, technology, function, and intended use.
• QC practices developed over the years have provided laboratories with some degree of assurance that results are valid.
• Newer devices have built-in electronic controls, and “on-board” chemical and biological controls.
• QC information from the manufacturer increases the user’s understanding of a device’s overall quality assurance requirements so that informed decisions can be made regarding suitable control procedures.

Quality Control (cont’d)

• Laboratory directors have ultimate responsibility for determining appropriate QC procedures for their laboratories.
• Manufacturers of in vitro devices have responsibility for providing adequate information about the performance of devices, means to control risks, and verifying performance within specification.
• In practice, QC is a shared responsibility of manufacturers and users of devices.

EP23 Laboratory Quality Control Based on Risk Management

MEASURING SYSTEM INFORMATION

- Medical Requirements for the Test Results
- Regulatory and Accreditation Requirements
- Measuring System Information
  - Provided by the Manufacturer
  - Obtained by the Laboratory
- Information About Health Care and Test Site Setting

PROCESS

Risk Assessment

OUTPUT

Quality Control Plan

PROCESS

Postimplementation Monitoring
Gather the Information
Laboratory Example

- fFN is a low-volume test (<2 samples/day)
- The need for daily liquid QC uses 2 cassettes ($100 each) and adds 40 minutes to turnaround time.
- Adoption of nontraditional TLI\textsubscript{IQ} would improve cost, test, and labor efficiency.

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TLi\textsubscript{IQ} Control Processes

- Automatic calibration with lot-specific code
- Three types of control processes:
  - QCette daily functional control cassette verifies that the analyzer performs within specifications.
  - Internal controls with each patient test verify the integrity of the sample and cassette flow by measuring the intensity of the control line.
  - Liquid controls with each shipment of cassettes qualify performance upon receipt.

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QCette

• More complex than an “electronic control”
• Comprised of a replica cassette containing preprinted test and control lines
• Goes through full read cycle by instrument
• Checks electronics, optics, and functionality of software algorithms to generate a value within predetermined specifications
  – **Procedural control line**: in high-positive range, must be above a minimum threshold
  – **Test line**: in the low range, must be within 5% of a value established at instrument setup
  – **Negative**: the white space between lines meets specifications to pass
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Internal Control Checks

- Performed with each test automatically
- Instrument checks light-emitting diodes, photosensor, and motor immediately before and after each test.
- Chemistry checks:
  - Minimal procedural control threshold
  - Adequate flow of conjugate
  - Adequate specimen volume
- Cassette “Pass” or “Fail” with “Invalid” result
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# TLiIQ Control Processes

<table>
<thead>
<tr>
<th>QCette</th>
<th>Internal Controls</th>
<th>Liquid Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daily</strong></td>
<td>Automatic with each test</td>
<td>Each shipment</td>
</tr>
<tr>
<td>Verifies analyzer</td>
<td>Verifies analyzer and cassette</td>
<td>Qualifies cassette and lot performance on arrival</td>
</tr>
<tr>
<td>performance within</td>
<td>performance during patient</td>
<td></td>
</tr>
<tr>
<td>specifications</td>
<td>testing</td>
<td></td>
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</tbody>
</table>
Developing a Quality Control Plan

Create a Process Map
(preexamination – examination – postexamination)

Identify weaknesses in the process

Define a process that will mitigate risk

Summarize Processes and Actions in a QCP
Where Is the Risk in Our Process?

Baseball Coach Loans Ferraris to Teenagers. What Could Possibly Go Wrong? April 1, 2009
Create a Process Map

Identify Weak Steps for Hazards or Risk of Error
Process Map: Finding the Weak Steps in the fFN Process

- Test order – electronic or hardcopy
- Test collection
  - False + – (bleeding, advanced dilation, sexual intercourse within previous 24 hours, range of motion, etc.)
  - Wrong swab/collection kit
  - Sample degradation – delay/temperature exposure
- Analysis
  - Incorrect calibration
  - Failure of reagent during storage
  - Wrong sample volume applied to cassette
  - Device failure during analysis
- Reporting results – transcription errors
Identify Potential Hazards

1. Samples
   - Sample Integrity
     - Lipemia
     - Hemolysis
     - Interfering substances
     - Clotted
     - Incorrect tube
   - Sample Presentation
     - Bubbles
     - Inadequate volume

2. Operator
   - Operator Capacity
     - Training
     - Competency
   - Operator staffing
     - Short staffing
     - Correct staffing

3. Reagents
   - Reagent Degradation
     - Shipping
     - Storage
     - Used past expiration
     - Preparation
   - Quality Control Material Degradation
     - Shipping
     - Storage
     - Used past expiration
     - Preparation

4. Laboratory Environment
   - Atmospheric Environment
     - Dust
     - Temperature
     - Humidity
   - Utility Environment
     - Electrical
     - Water quality
     - Pressure

5. Measuring System
   - Instrument Failure
     - Software failure
     - Optics drift
     - Electronic instability
   - Inadequate Instrument Maintenance
     - Dirty optics
     - Contamination
     - Scratches

Incorrect Test Result
Conduct a Risk Assessment

Identify Control Processes for Each Hazard That Maintain Risk to a Clinically Acceptable Level
Risk Assessment

• Specimen
  – Improper sample collection – YES – Physician education
  – Wrong tube or clotting – NA – special collection kit
  – Specimen delay – YES – monitor transport conditions
• Operator
  – Too much or too little sample application – YES – $TLi_{IQ}$ onboard controls, and use of dedicated pipette.
  – Incorrect timing/interpretation – NA – automatic device
  – Training/competency – Minimal – medical technologist staff in laboratory
  – Transcription error – YES – double check results
  – Incorrect operation – NA – automatic device

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Risk Assessment (cont’d)

• Reagent
  – Test exposure outside specifications (temperature, humidity, etc.) – YES – *analyze QC samples with each shipment*
  – Wrong calibration – NA – *autocalibration lot numbers*
  – Expired reagents – YES – *barcoded cassette prevents use past expiration date*

• Environment
  – Core laboratory – Minimal – *no other errors noted in past for similar methods/readers*

• Analysis
  – Electronic/system failure – NA – *TLi_{IQ} checks*
  – Result drift – YES – *monthly liquid QC – reagent viability*

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Evaluation of TLI IQ

- Two levels of QC daily for one month (N = 20)
- QCette daily
- Minimum manufacturer’s recommendations followed for assessing TLI IQ acceptability
- Two levels of QC and QCette passed
- One exception: liquid negative control invalid due to an internal cassette failure (sample did not migrate)
- Repeated successfully on new cassette

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Examination of the TLIQ System Nontraditional Quality Control for Rapid Fetal Fibronectin Testing

Laura Fellows, CLS(C) (NCA), James H. Nichols, PhD, DABCC, FACB, and Simon Shorter, PhD

Fetal fibronectin (fFN) is a placental protein used to assess the probability of delivery in women at high risk for preterm labor. Qualitative fFN in vaginal secretions is available on the TLI analyzer (Adea Biomedical Corp., Sunnyvale, CA). A recent update to the TLI analyzer, termed the TLIQ, eliminates the need for daily calibration and the daily performance of two levels of liquid quality controls through the use of lot-specific calibration codes and the TLIQ QCette cartridge. The TLIQ QCette cartridge is a replica cassette containing a membrane with preprinted lines that undergoes a full measurement cycle to determine analyzer response at multiple levels (negative, low, and high). Parallel measurement of liquid controls with the new TLIQ functional QCette (N = 20 over 30 days) demonstrated no discrepancies. On one day, the negative liquid control errored as invalid because of an internal cassette failure (did not migrate). Accuracy was assessed with known positive (N = 10) and negative samples (N = 10) without discrepancy. By eliminating the daily calibration and liquid control steps, implementation of the TLIQ analyzer has had a significant impact on staff efficiency, workflow, and result turnaround time, without compromising accuracy of the test results.

Key Words: Fetal fibronectin—Maternal/fetal testing—Maternal/fetal risk assessment.

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Risk Assessment

• Clinical Application
  – Immediate medical decisions – YES – internal TLiIQ controls with each test, in-house 30-day comparison to external QC verifies process stability
  – Stability of sample – sample stable for retest

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Summarize the Quality Control Plan
Quality Control Plan

- Analyze QC:
  - Each new shipment*
  - Start of a new lot*
  - Monthly
  - Whenever uncertainty exists about cassettes*
- Use QCette each day*.
- Use internal controls with each test*.
- Provide physician education on collection, false-positive sources.
- Ensure courier refrigerates samples and monitors transport times.
- Use dedicated 200-microliter pipette for sample application.
- Use checklist to document training/competence/maintenance.

(* Manufacturer recommendations)
Implement the Quality Control Plan
Monitor for Failure/Errors and Modify Quality Control Plan as Needed
Plan Implementation: Quality Monitors

- Number of complaints: false positives/retests
- Frequency of test cancellation – specimen received using wrong swab/collection kit
- Liquid QC failure rates
- Frequency of device error codes
- Any other unexpected error
Where Is the Risk in the Process?

What could possibly go wrong?
Summary

• A QCP summarizes potential device errors and how the laboratory intends to address those errors.
• A QCP can be high level or very detailed depending on the device, the laboratory, and the clinical application of the test result. The results may vary from one laboratory to next.
• The QC plan is scientifically based. It depends on the extent to which the device’s intended features or actions achieve its intended purpose in union with the laboratory’s expectation for ensuring quality test results.
• Once implemented, the quality control plan is monitored for effectiveness and modified as needed to maintain risk at a clinically acceptable level.
Don’t Be Discouraged—Risk Management Is Documenting Much of What We Already Do!
EP23 Companion Products

EP23-A
Implementation Workbook
A Practical Guide for Laboratory Quality Control Based on Risk Management

Plus – More fully worked examples coming soon to www.clsi.org
Questions?