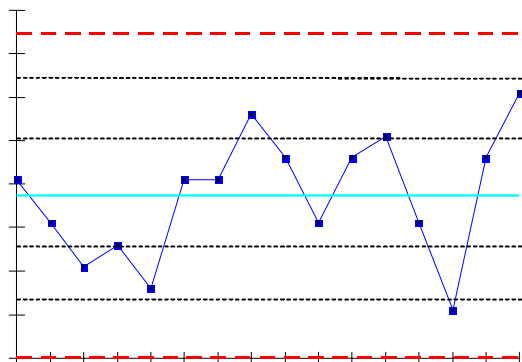


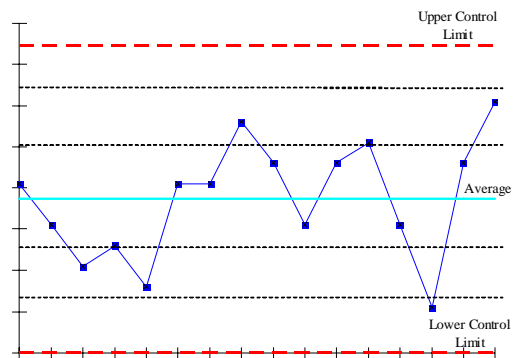
Uncertainty in Measurement (UM)

Guideline Review for Medical Labs

Is This Process in Control?



How About Now?



Yes, it is in a state of control

- It varies predictably.
- It does not exceed control limits.
- It does not violate any statistical charting rules.

And that's where U in M comes in...

- Makes good clinical sense
 - Helps us see the normal from the abnormal
- Mandated by ISO 15189 (5.6.2)
 - Which brings us together today
- A product of the ISO Uncertainty in Measurement task group.
 - Subset to the MedTAC
 - Thanks to them, especially Deborah Miller.
 - Thanks to others, especially Dan Tholen.

Uncertainty in Measurement

Parameter, associated with the result of a measurement, which characterizes the dispersion of values that could reasonably be attributed to the measurand.

So let's get it started...

- Introduction to the need for uncertainty in measurement.
- Terms associated with uncertainty in measurement.
- Implementation of action steps to help our clients.
- Monitoring of UM estimates.



Feel the Need...

- “Are these results different?”
- Variation is inherent.
- Allows practitioner to understand trueness of value.
- Leads to better understanding of clinical condition.



Two-sided coin

- By understanding the amount of uncertainty in a measured value:
 - A clinician can better understand the fitness of use of that measurement for clinical purposes.
- By controlling the amount of uncertainty in a measured value:
 - A laboratory can have assurance of accuracy in its method.

Two Sources of Uncertainty

The Calibrator

- May be provided by manufacturer.
- If not, then it's all about you.

Common Cause

- Random error
- Imprecision
- Generally obtained from internal quality control data.

Lots of Differences, Lots of Testing



- To establish common cause, include testing with:
 - Different operators
 - Different shifts
 - Different equipment
 - Different lots (over time)
 - Different locations (if applicable and desirable).

Talk the Walk

- Terms Associated with Uncertainty of Measurement



Brief Review of Terms

- Accuracy: closeness to the true value.
- Analyte: Informal term to identify substance measured.
- Analytical Goal: Accepted target uncertainty.
- Bias: Analytic error of a test system determined by repetitive measurements.
- Error: Difference between the measured value of the measurand and the true value of the measurand.
- Examinations: Clinical tests.
- Imprecision: Expressed variation.
- Measurand: Property of a substance being measured.

More Brief Review of Terms!

- Numerical Significance: Figures of a number that have practical meaning.
- Precision: Closeness of expressed variation.
- Proficiency Testing: Inter-lab comparisons to monitor performance of a lab.
- Standard International Units: Metric Units adopted by all major countries for a variety of purposes.
- Traceability: Relate a measured value through an unbroken chain to a reference standard.

Walk the Talk

- 8 Steps to achieve a UM program



Step 1: Categorize Examinations

- Identify all examinations within scope.
- Map into:
 - Category 1: Methods reported on a qualitative basis or on a categorical or nominal scale.
 - Category 2: Well-recognized test methods that use kits or prepared reagents to determine qualitative results that are on an ordinal scale.
 - Category 3: Well-recognized quantitative and semi-quantitative methods governed by the FDA approved test systems.
 - Category 4: In-house developed tests.



Category 1: Up close and personal

- Provides an attribute answer to the examination inquiry.
- Not kit driven.
- UM not meaningful as variation is due in large part to technical competency and not to inherent measurement in and of itself.
- Does not include ordinal data: +, ++, +++
- Does not include identification, such as Bac-T.

Category 2: Up close and personal

- Uncertainty estimates satisfied by following published method, meeting performance requirements (PT), and subsequent reporting.
- All the components of analysis of the kit fall under FDA purview.
- FDA approves the insert for human testing.
- Manufacturer controls versions of inserts.
- Examples: RPR, RBC Antibody panels

Category 3: Up close and personal

- UM must be determined.
- Typically use internal QC data for estimate.
- May provide a qualitative result based on quantitative responses.
 - Particularly in terms of indeterminate responses close to the cut-off of the test method.
 - UM expressed as one or more of the following:
 - UM statement for samples at levels near the cut-off.
 - Statement concerning false classification rates for results near the cut-off.
 - Overall rates of correctness for different known classes of samples.

Category 4: Up close and personal

- UM must be estimated using:
 - Available data
 - Published information
 - Design of Experiments (DOE)
- These are “and/or” criteria.

Step 2: Define the Measurand

- For examinations requiring UM.
- Documentation exists for:
 - The analytical method used.
 - The substance measured.
 - The characteristic measured.
 - The diagnostic limitations of the method.
 - Any cross-reactivity or interfering substances that impact clinical interpretation.



Step 3: Identify components of UM

- Two sources of uncertainty to consider:
 - Normal variation (imprecision) associated with running the method repeatedly.
 - Common cause
 - Standard Deviation (SD)
 - Uncertainty associated with the calibrator.
 - May be negligible
- What contribution is what? And does it matter?



Step 4: Record Mean Long Term Imprecision QC Data as UM Estimate

- Standard Deviation (SD)
- Coefficient of Variation (CV)
 - Both may provide the UM estimate.



Old v. New

Established Methods

- Collect at least 6 months of internal QC data
- Calculate SD or CV
- Multiply by ± 1.96 to provide confidence interval.
 - 1.96 is the critical z value for 95% confidence from the t distribution of critical values.

New Methods

- Collect at least 30 data points for each level of QC using:
 - At least 2 different lots of calibrators.
 - At least 2 different lots of reagents.
 - This is short term UM; long term is recalculated as data are collected.
 - Multiply by ± 1.96 to provide confidence interval.

The more data evaluated, the more reliable the estimate.

Step 5: Establish Analytical Goal

- Value of the measurand coupled with UM should be compared to a biological reference value or clinical decision limit.
- How much imprecision is the lab willing to accept in terms of the biological variation of the analyte?



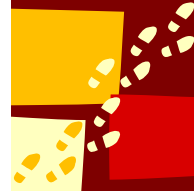
Step 6: Determine Numerical Significance of UM Estimate and Clinical Results

- Lab establishes what represents meaningful differences in values.
- Done by evaluating imprecision data.
 - If tight (little variation), numerical significance is greater.
 - If loose (big variation), numerical significance is less.



Step 7: Interface with Clinicians

- Lab determines with clinicians :
 - Results that could impact clinical interpretation and patient management.
 - Reporting necessity of UM estimates in actual patient reports.
- Lab must have method to inform clinicians of significant UM estimates in a meaningful way.



Step 8: Monitor the Program

- The more time, the more data, the more stable the estimate.
- For each examination with a UM estimate, a monitoring program must exist.
 - Sampling Plan
 - Monitoring Rules
 - Actions to Maintain Estimate



Sampling Plan

- When QC data will be collected
- Where QC data will be collected
- How QC data will be collected.
 - Includes how many measurements will be part of the sample.
 - Dictates the type of chart used for monitoring.
 - Generally, all QC and PT data should be used to evaluate the established estimate of UM.

Rules of Monitoring

- Apply statistical rules to ensure processes exhibiting common cause.
 - What rules will apply? Which will not?
- Actions must be defined that result when UM concerned examinations are not functioning within a state of statistical control.

Actions to Maintain Estimate

- Root cause analysis (meaningful)
- Subsequent corrective action
- Communication and documentation of changes in the UM

- Remember, it may change over time as processes improve!

Let's get it finished!

- Introduction to the need for uncertainty in measurement.
- Terms associated with uncertainty in measurement.
- Implementation of action steps to help our clients.
- Monitoring of UM estimates.



So, two guys to into a bar...

- One has a glucose of 110.
- One has a glucose of 112.

Who's normal? Who's not?

It all depends!



Questions?