ISO 15189:2012 5.5.1.4

Measurement of Uncertainty

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Content of presentation

- What is it?
- Environmental factors
- Quantitative
- Case study as a user
- Qualitative with examples of process
- Traceability
- Easy option
- Questions

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What is it?

Cast your mind back to being an MLSO on various tests.

Examples

Hb estimation- cut off value for making blood films in antenatal patients.

B12 estimation by Lactobacillus leismannii

Osmotic fragility

Variation in the final result-What effect does it have on the reported result- and what does it mean for the patient

How CERTAIN were you of these results

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Pre-examination

- Many are in existing SOPs as limitations
- Patient state
- Patient Prep
- Time of collection
- Collection site
- Method of collection
- Sample transport
- Sample storage prior to testing

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Post exam

Others to consider

Use of 3rd party results- can also be pre-exam

Calculations

Reporting- round up/down

Reference ranges

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MU or UM?

5.5.1.4 Measurement uncertainty of measured quantity values

The laboratory shall determine measurement uncertainty for each measurement procedure **in the examination phase** used to report measured quantity values on patients' samples. The laboratory shall define the performance requirements for the measurement uncertainty of each measurement procedure and regularly review estimates of measurement uncertainty.

NOTE 1 The relevant uncertainty components are those associated with the **actual measurement process, commencing with the presentation of the sample to the measurement procedure** and ending with the output of the measured value.

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Limitations

pre and post limitations- not uncertainty under 15189

will come under other clauses- risk and preventative actions as well as Pre-exam (5.4) and post exam (5.7)

If there are limiting activities, would expect some control

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Quantitative

Many statistical methods can be used

Data from repeated samples, EQA, IQC

CV, SD, confidence limits, probability…

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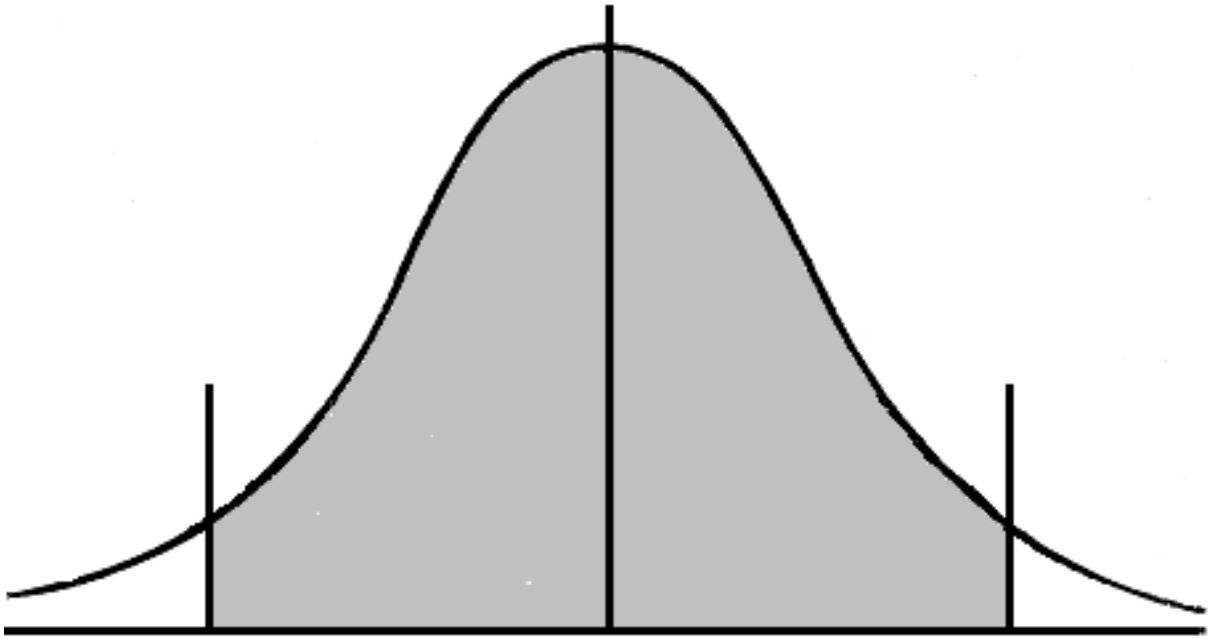
Quantitative

Normal distribution curve



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Example from SD

Mean

$$\bar{x} = \frac{x_1 + x_2 + x_3 \ldots x_n}{n}$$

Standard deviation

$$s = \sqrt{\frac{\sum (x-\bar{x})^2}{n-1}}$$

Standard uncertainty

$$U_i(x) = s(x)$$

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Excel

Programs on Excel- DATA ANALYSIS

Add-in-

File-Options-add ins

Descriptive statistic

Mean

SD

Variation

Annova- two columns of figures.

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Approximate statistical relationships

SD	Confidence level	Coverage factor
1	90%	1.65
2	95%	1.96
3	99%	2.58

Expanded Uncertainty

$U = Ui \times 1.96$

$k=2$

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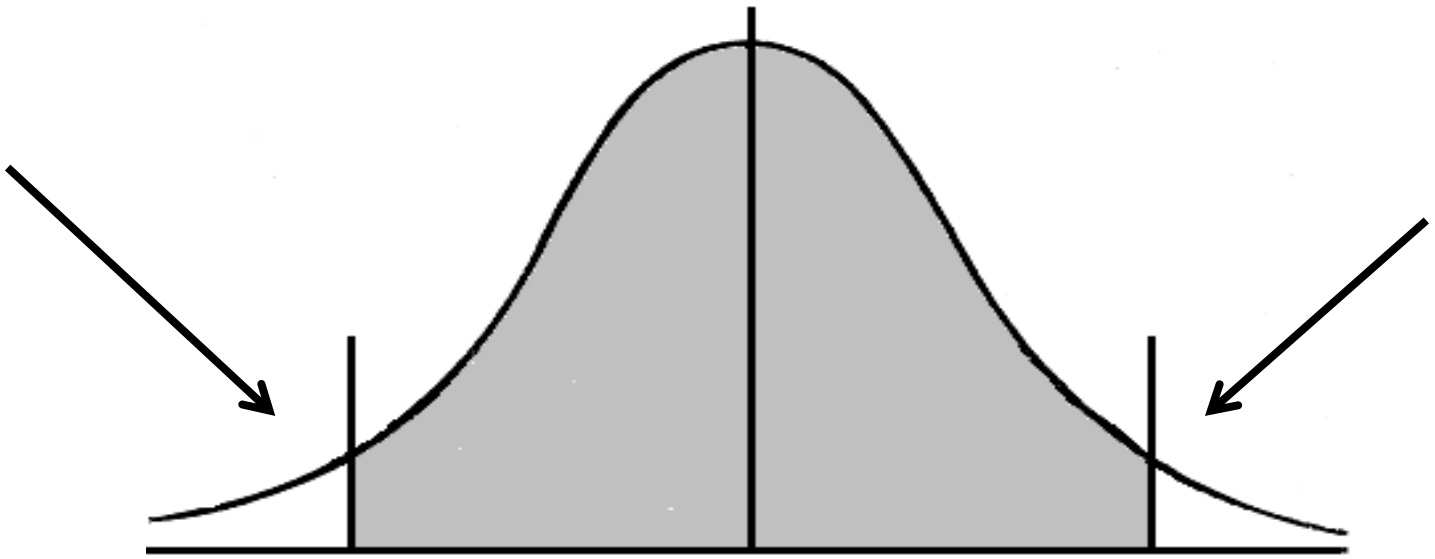
The end bits

Normal distribution curve



X= +/-

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Other considerations

Bias
Type A and B sources
Traceability
Uncertainty Budget-combined uncertainty

- $\sqrt{\Sigma (U_{1..n})^2}$

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Traceability relationship- back to standards

Some examples are;-

National Physical Laboratory - UK

National Institute of Standards and Technology – USA

- **Physikalisch-Technische Bundesanstalt – Germany**
- **World Health Organization (WHO)**
- **NIBSC**
- **SI base units and derived units**

The further away the traceability- the more uncertain the measurement

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Confidence in results

What is acceptable?

What is the reliability of the exam procedure

What has influence on the reported result?

What does it mean to the user?

Does it alter the patient care?

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Case Study from a User perspective

CHARLIE

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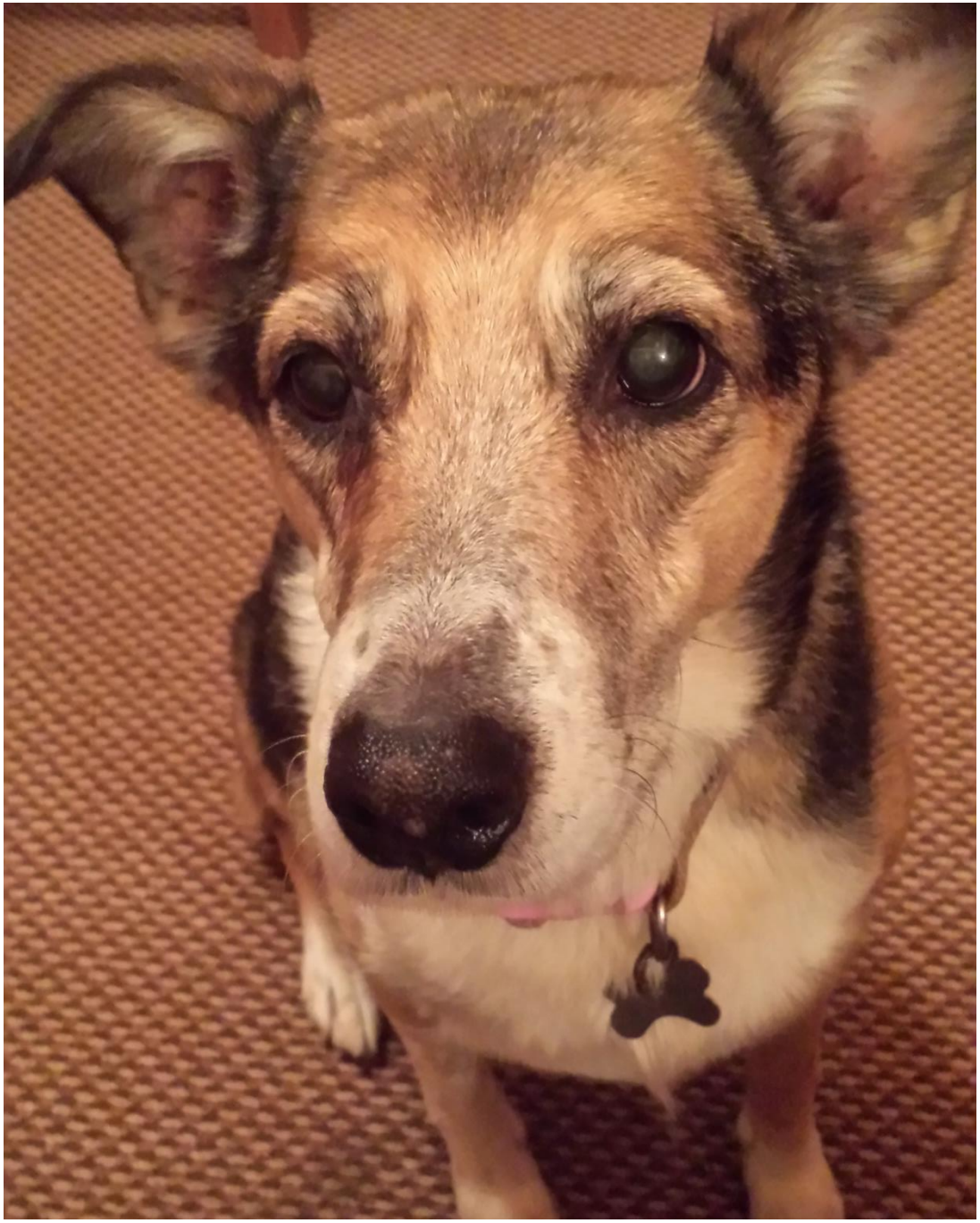

Cushing's Disease

Initially blood sample every month- now every 6 months- approximately £70 per sample.

Currently on Vetoryl® (trilostane) 60mg twice daily- 12 hours apart. Sample to be taken off 4 hours after dosage.

Cost of Vetoryl®- 60 tablets, one months supply ;-

120mg=£146.40

60mg=£90

30mgs=£71.40

10mgs= 56.40

Vets only prescribe a two month supply

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On day of blood test

Charlie given 60mg at 7am

Appointment at vets for 11am

Arrived 10.50am

Charlie not seen until 11.30, unknown when sample taken off

Vet unhappy as it has been more than 2 months since last prescription

Owner admitted forgetting to give Charlie tablet on occasions, but twice a day for past fortnight.

Charlie running around like a 2 –year old.

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Results

Owner told results can take a day or two-vet will phone

Vet phoned next day and told owner over phone- Charlie is out of control.

But continue on the 60mg dose, and wants to see her in 2 months time instead of 6.

If dosage requirements is increased to 70mg/twice daily, cost almost doubles

Charlie looks well, eating well and weight stable.

SO WHAT SHOULD OWNER ASK?

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What does it mean to the User

- Was the blood sample taken exactly 4 hours after dosage? Does this time lapse alter results?
- What was the actual result?
- What was it previously?
- What are the reference ranges used- manufacturer, dog breed specific, area specific
- What calibrator was used and is it traceable?
- How is result V dosage worked out?
- Does the vet want another £70 for a blood test in two months time instead of 6?
- Do they have 17025 (testing) accreditation?

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Qualitative

Results given out as

Positive or Negative

Present or absent

Yes or No

Most likely there are some measurement steps in the process arriving at conclusions e.g.;-

- **Any step which is timed**
- **Any step which includes temperature**
- **Any step which includes volume dispensing**

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Quantitative steps

Are these measured steps a critical part in your process?

If it says dilute 1/10, does diluting 1/20 or 1/5 affect your final result?

If you have to fix a smear for 20 minutes, can you cut corners and fix for 5 minutes less.

Does incubate at 37◦C mean round about 37◦C

At what measurement level of these steps can you be certain of your result that it would not change the treatment of the patient?

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Positive or negative

Many consider that MU is not applicable

BUT

At what level /concentration/number tips a negative into positive result and vice versa?

Limit of detection should be considered for you to be certain of a result.

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Kleihauer acid elution test for detection of HbF cells.

Screening test comes out as present or absent- so what could go wrong

Steps

Make control of 1:100 foetal/male blood samples

Add 2 drops of PBS

Mix well

Make slides to produce a good monolayer of cells

Dry for 20 minutes , but not under heat

Fix for 3 minutes

Add elution reagent for 30secs

Counterstain for 2 minutes

If less than 4 foetal cells seen, consider as negative

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Critical steps in processes

Determine what steps in your processes are critical to ensure that the end result is not altered.

If there is a volume step- have your pipettes been calibrated by a 17025 (calibration) accredited company.

If temperature critical, has you temperature monitoring calibration traceable back to national standards.

If so, the certificate will state *k*=2, which goes back to 95% confidence limits- 2.5% on either side of value- does your process work within these limits.

If your process step works outwith 5% limits, step may not be critical

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Operator variability

Manual process will incur differences between operators

Statistical methods can be applied to repeated results e.g. manual white cell differential counts, any manual cell counts

Macroscopic and microscopic measurements in Histo

Cell counts

Even with simple processes like “dipstick “ tests, results can be repeated by operators and statistics performed on them.

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Manufacturers instructions

Each kit method should be verified for use in your laboratory

Limit of Detection should be considered- would probably be in a verification

CE marking does not guarantee kit performance in your lab

Each step needs to be looked at to see what any variation would influence on the reported result.

If its an in-house test- validations should have been performed and uncertainty steps considered.

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Documenting

- Entirely up to lab
- Some overarching SOPs, but need to consider influence on each result and documented somehow
- Could be an appendix to each SOP, or under “Limitations”
- Quantitative can be used in tables for reference when required.
- Upon request…available to users

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Variation and reliability

Each step of a procedure has some degree of variability or variation

- Variation is measurable
- Variation has an accumulative effect
- Accumulated variation can influence results interpretation

On going activity- How often?- how stable is your process?

Is the end result reliable to the point it will not adversely affect the patient treatment or influence on the reported result or do you know the measurement uncertainty that will?

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As Promised

Easy Option

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TRUE SCOTS KEN THAT
"A BAW HAIR" IS
A UNIT O MEASUREMENT

Further reading

References used;-

ibms website- John Wood presentation

Eurachem/Citac QWAG/03/06 2003 paper

The Hitch-hiker's Guide to Measurement Uncertainty (MU) in Clinical Laboratories

Information available on UKAS website: 'Publications for Laboratory Accreditation to & 'Technical Policy Statements'

PD ISO/TS 20914:2019-Medical laboratories — Practical guidance for the estimation of measurement uncertainty

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Thank you for your attention

Any Questions?

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