

2025
EEMEA
SCIENTIFIC
SEMINARS

Measurement Uncertainty and the Haemostasis Lab

Stephen MacDonald

Consultant Clinical Scientist

Cambridge University Hospitals NHS Foundation Trust

16th Advanced
Hemostasis Seminar

October 14-15, 2025 • Vilnius



werfen

INTERNATIONAL
STANDARD

ISO
17511:2020

ISO 17511:2020 - In vitro diagnostic medical devices - Requirements
for establishing metrological traceability of values assigned
to calibrators, trueness control materials and human samples

INTERNATIONAL
STANDARD

ISO
15189

Third edition
2013-11-01
Corrected version
2014-08-15

**Medical laboratories — Requirements
for quality and competence**

*Laboratoires de biologie médicale — Exigences concernant la qualité
et la compétence*

INTERNATIONAL
STANDARD

ISO
22367

First edition
2020-02

**Medical laboratories — Application
of risk management to medical
laboratories**

*Laboratoires de biologie médicale — Application de la gestion des
risques aux laboratoires de biologie médicale*

TECHNICAL
SPECIFICATION

ISO/TS
20914

First edition
2019-07

**Medical laboratories — Practical
guidance for the estimation of
measurement uncertainty**

*Laboratoires médicaux — Lignes directrices pratiques pour
l'estimation de l'incertitude de mesure*

Why?

- “....various potential benefits for the laboratory and the organisation....”¹
- “.....these include a better understanding of assay limitations”¹
- Clinical decisions are made with an awareness that:
 - variability is present in results
 - variability is being controlled by the laboratory
 - to a clinically acceptable level of risk

1. Favaloro, E. J. (2006). Uncertainties in Measurement of Uncertainty Measurements: A Commentary from the Perspective of a Specialist Haemostasis Laboratory. Australian Journal of Medical Science, 27(2), 72–83. <https://search.informit.org/doi/10.3316/informit.182099435319554>

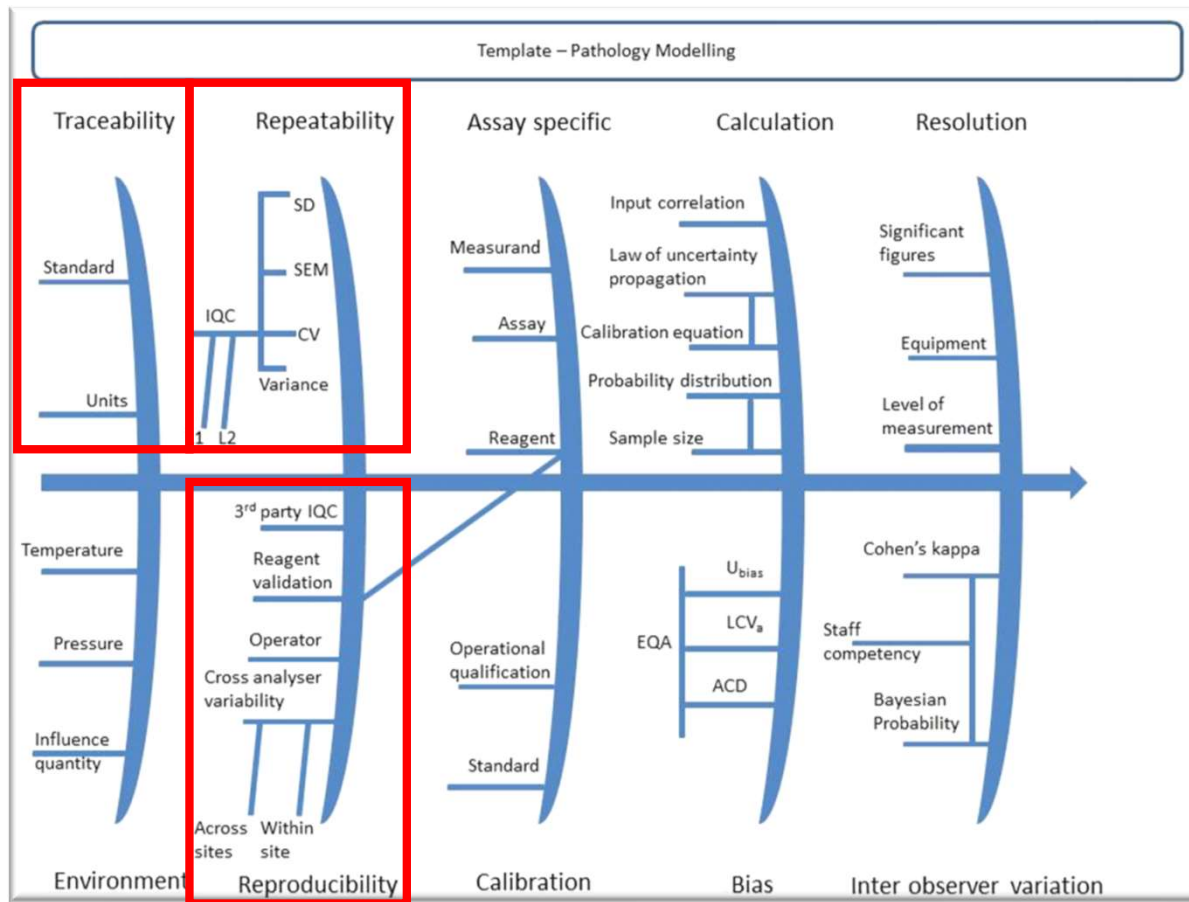
2022 Highlights ¹ – MU shall be.....

- Evaluated and maintained for its intended use
- Regularly reviewed
- Rationale for exclusion of MU shall be provided
- Made available
 - Include biological variation....
- Semi-Quantitative – assess the steps involved
- Qualitative
- Verification and Validation
- Lots of “where relevant” ¹
- “Regular” ¹
- A hint to where we can find ways of approaching it
 - ISO/TS 20914:2019 ²

1. Summary based upon ISO15189:2022, summary based on presenters opinion

2. ISO/TS 20914:2019 – Medical Laboratories – Practical Guidance for the estimation of measurement uncertainty. BSI Standards Publication, 2019

The old way – the GUM



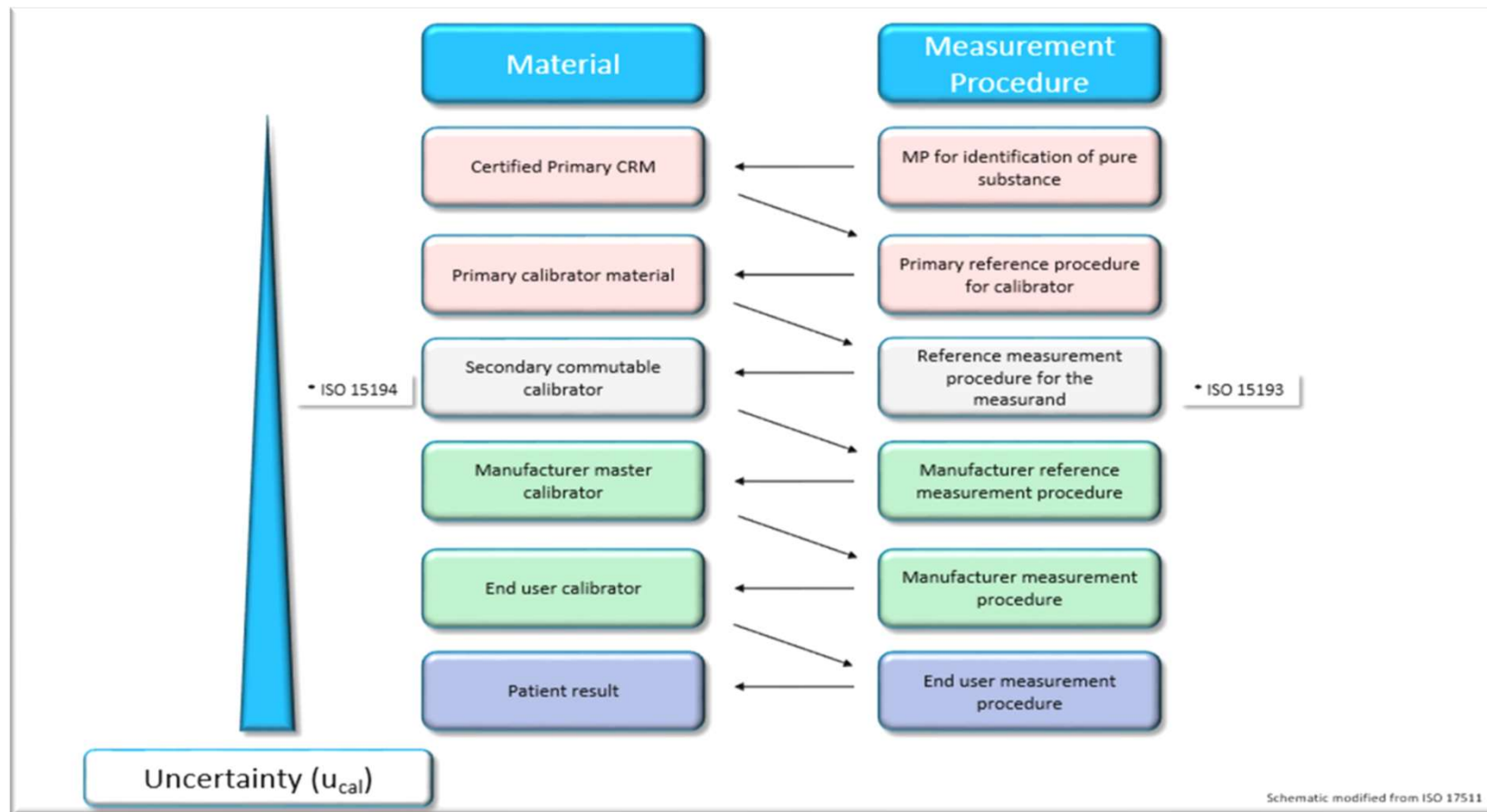
$$u_c^2(y) = \sum_{i=1}^N \left(\frac{\partial f}{\partial x_i} \right)^2 u^2(x_i) + 2 \sum_{i=1}^{N-1} \sum_{j=i+1}^N \frac{\partial f}{\partial x_i} \frac{\partial f}{\partial x_j} u(x_i, x_j)$$

Image available at: <https://www.nist.gov/pml/nist-technical-note-1297/nist-tn-1297-appendix-law-propagation-uncertainty>

Image and articles available at: <https://www.pathologyinpractice.com/>.
Image developed by presenter 2017

IQC – Internal Quality Control, L1 – Level 1, L2 – Level 2, SD – Standard Deviation, SEM – Standard Error of the Mean, EQA – External Quality Assurance, ubias – bias uncertainty, LCVa – Long Term Analytical Variation, ACD – Analytical Critical Difference, GUM – Guide to the Uncertainty of measurement, JCGM 100:2008

The “new” way – Top-Down method – but not just a CV!



u_{cal} – uncertainty of the assigned value of the calibrator, CRM – Certified Reference Material, MP – Measurement Procedure,
CV – Coefficient of Variation

Schematic developed by presenter, modified from ISO 17511

Why the Top-Down method? ¹

$$u(y) = \sqrt{u_{\text{cal}}^2 + u_{\text{bias}}^2 + u_{\text{Rw}}^2}$$

- Less mathematically intensive than the GUM method
- Has been shown to perform comparably...to an extent ²
- It uses data already available as part of our quality management processes
- No need for additional experiments.....for the most part ¹
- The assumption is:
 - All contributors that are considered significant will be “captured” by local laboratory variability detected by internal quality Control Processes ¹

1. Presenters own opinion

2. Lee, Jun Hyung, Choi, Jee-Hye, Youn, Jae Saeng, Cha, Young Joo, Song, Woonheung and Park, Ae Ja. "Comparison between bottom-up and top-down approaches in the estimation of measurement uncertainty" *Clinical Chemistry and Laboratory Medicine (CCLM)*, vol. 53, no. 7, 2015, pp. 1025-1032. <https://doi.org/10.1515/cclm-2014-0801>

GUM – Guide to the Uncertainty of measurement, JCGM 100:2008

Simple – right.....??

$$u(y) = \sqrt{u_{\text{cal}}^2 + u_{\text{bias}}^2 + u_{\text{Rw}}^2}$$

- What if you haven't got intermediate precision (IQC) data that is representative of your process over time?
- “MU should be taken into consideration when performing verification or validation of a method, when relevant”¹
 - What is an interim estimate?
- There seems to be a new parameter creeping in.....²

The most common question I get asked.....¹

$$u(y) = \sqrt{u_{\text{cal}}^2 + u_{\text{bias}}^2 + u_{\text{RW}}^2}$$

- “How often do you recalculate MU?”
- 15189:2022 - “MU evaluations shall be regularly reviewed” ²
- The simple answer - “....around 6 months”
- This is the period – alluded to throughout all medical lab MU that permits robust statistical data for u_{RW} estimation BUT.....
- It’s the wrong answer to the wrong question

1. Presenter’s own experience

2. ISO15189:2022 7.3.4

The most important line in the whole ISO document!

$$u(y) = \sqrt{u_{\text{cal}}^2 + u_{\text{bias}}^2 + u_{\text{Rw}}^2}$$

- “Apart from updating interim estimates.....”¹
- “...there is no need to re-estimate MU if IQC and EQA performance remain within specifications”¹
- This single, simple sentence is actually THE WHOLE POINT of MU!

1. ISO/TS 20914:2019 section 6.8

Validation and Verification

- Evidence for assay being acceptable.....clinically
- We have a budget we must not exceed
- Repeatability studies dictate the early conformance to the MU requirements ¹ – they are then used as interim MU, updated when u_{RW} is available ²
- We can only do so much in the lab
- If we exceed our limit – the manufacturers may have to change their calibrator “quality”
- And even our international standards may have to be reviewed ²

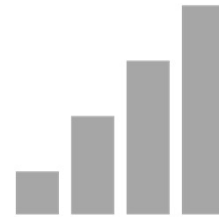
MU – Measurement Uncertainty, u_{RW} – Uncertainty of the random variation within laboratory/within laboratory precision

1. CLSI EP29A – Expression of Measurement Uncertainty in laboratory Medicine – Approved Guideline, CLSI, 2012

2. Presenter's opinion

Interpretation

- Specifications are dependent on adequate data being available
 - Clinical Outcome
 - CV_I and CV_G – Biological variation
 - What is achievable – State of the Art
- That determines whether a method is “good enough”
 - -> The quality of the method (Variability in results is controlled to an acceptable level of risk)
- So does interpretation – The Reference Change Value (RCV)
- Incorporates CV_A (but more and more now actually U_c)



QC to MU

MU is just imprecision.....right?
The all singing all dancing CV..?



The purpose of QC

I – Checking the alignment of the system

- Reject/accept a run based on:
 - Routine operations
 - Verification of traceability
 - Material provided by from suppliers with assigned values
- Conformance by results being within a range

II – Checking the stability of the system

- Estimating the random effects that contribute to MU
- Should it be 3rd party only?
- Conformance with rules such as multirules, sigma rules

QC for MU- what do we need?

Imprecision

- Commutability
- Traceable
- Clinical Decision levels
- Represent long term variations in a process
- QC picks up the variability that we would need to quantify to do a more “metrological” approach

Bias (and its correction)

- Are we different from the “true” value
- Traditionally EQA (consensus value or traceable assigned value)
- But also
 - CRM (if available)
 - Peer review IQC

So.....how do we think we represent this in the best way – we have an IQC process.....



Which of these best describes your QC frequency?

1. Once in the period of time the Earth takes to rotate round its axis?
2. The time taken for the Sun to reach its highest point two consecutive times divided by 3?
3. The first available time after the upper rim of the Sun appears over the horizon?
4. Half the time the Earth rotates on its axis with reference to a specific star?

Do our QC processes genuinely fit the purpose of what we need for MU estimation?



Do they REALLY represent variation in the system?



Specifically for every assay individually?



How much bias are WE introducing into the system?



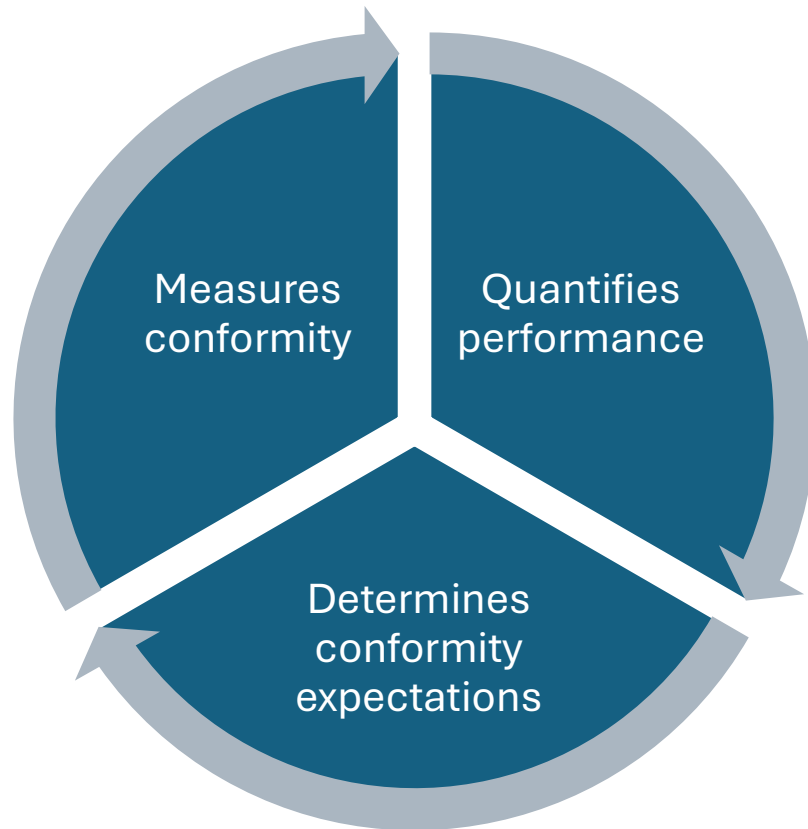
Are we (can we..) account for this issue?

The answers to the last few questions will have a massive impact on how easy things are for MU and IQC

Assumptions

- Normality of IQC and errors 
- Random 
- Independence 
- Combination of variances 
- Heteroscedasticity 

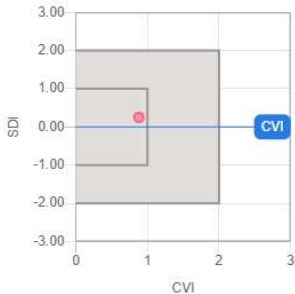
Sense check – how do we stop it becoming a self fulfilling prophecy?



- Who do you compare against?
- Nobody
- Somebody

Lab Performance plots

CONTROL	TEST	UNIT	SYSTEM GROUP	SN / MODEL
HemosIL Normal Control ASSAYED	PT- RecombiPlasTin	seconds	ACL TOP Family	(14120102) ACL TOP 750 CTS
LOT: N1108804				
REAGENT LOT: N0403055				
SDI: 0.25				
CVI: 0.88				



Message/Exception Summary

Laboratory: 29584
Cambridge University Hospitals Nhs
Box 217
Cambridge CA
Report period: 03/01/22 - 03/31/22
Comparison area: Worldwide

Message / Exception Summary

werfen

ATTACHED ARE YOUR ACCUTRAK 2.0 QC REPORTS. WE HAVE LISTED ANY 'EXCEPTIONAL' OCCURRENCES IN YOUR PROGRAM THIS MONTH. FOR ASSISTANCE IN INTERPRETING ACCULERT MESSAGES, PLEASE CALL TECHNICAL SUPPORT at (800) 678-0710.

The following messages are based on the statistical analysis of your data compared with your peer group (Test/System/Method) and do not necessarily indicate a quality control problem. They are strictly statistical in nature. It is up to the laboratory to determine clinical significance. Please note: for a normal distribution 95% of labs will fall within 2SD of the mean and 5% are expected to fall outside the 2SD range.

CONTROL	TEST	SN / MODEL
HemosIL Normal Control ASSAYED	Factor VII	(14120102) ACL TOP 750 CTS
LOT	MESSAGE	
N1108804	"N0403055" Reagent Lot will expire on "04/30/22".	

SDI plots

CONTROL		CONTROL LOT	REAGENT LOT	TEST	UNIT	SYSTEM GROUP	SN / MODEL							
HemosIL High Abnormal Control ASSAYED		N1209113	N0411921	APTT-SynthASil	seconds	ACL TOP Family	(14120102) ACL TOP 750 CTS							
YOUR DATA						PEER GROUP				SDI RANGE				
MONTH	N	MEAN	1SD	CV	SDI	LABS	MEAN	PSD	CV	-3	-2	0	+2	+3
Mar	50	53.72	1.08	2.01	-1.83	10	55.26	1.36	2.46					
Feb	45	53.92	0.92	1.71	-1.82	10	55.36	1.36	2.45					
Jan	43	54.25	1.01	1.86	-1.80	10	55.40	1.26	2.28					
Dec	23	53.50	0.90	1.68	-0.09	14	53.61	1.27	2.37					

Have we got a bias?

CONTROL		CONTROL LOT	REAGENT LOT	TEST	UNIT	SYSTEM GROUP	SN / MODEL										
HemosIL Normal Control ASSAYED		N1108804	N0403055	Factor V	%	ACL TOP Family	(14120102)	ACL TOP 750 CTS									
YOUR DATA								PEER GROUP			SDI RANGE						
MONTH	N	MEAN	1SD	C.V	SDI	LABS		MEAN	PSD	C.V	-3	-2	0	+2	+3	COMMENTS	
Mar	5	96.70	3.86	3.99	0.93	2		95.33	4.26	4.46							
Feb	6	96.28	3.79	3.94	0.70	2		95.83	4.06	4.24							
Jan	5	97.10	1.93	1.99	0.71	2		93.27	3.09	3.31							
Dec	8	97.60	4.00	4.10	0.35	2		96.32	3.57	3.71							
Nov	7	99.07	3.14	3.17	0.65	2		97.05	3.61	3.72							
Oct	6	98.40	1.08	1.10	0.83	2		96.65	2.59	2.68							
Sep	4	95.95	2.10	2.19	-0.89	2		96.11	4.23	4.40							

CONTROL		CONTROL LOT	REAGENT LOT	TEST	UNIT	SYSTEM GROUP	SN / MODEL										
HemosIL Normal Control ASSAYED		N1108804	N0403055	Factor V	%	ACL TOP Family	(15010104)	ACL TOP 750 CTS									
YOUR DATA								PEER GROUP			SDI RANGE						
MONTH	N	MEAN	1SD	C.V	SDI	LABS		MEAN	PSD	C.V	-3	-2	0	+2	+3	COMMENTS	
Mar	12	94.76	4.39	4.63	-0.39	2		95.33	4.26	4.46							
Feb	6	95.37	4.32	4.53	-0.72	2		95.83	4.06	4.24							
Jan	5	89.44	3.92	4.38	-0.71	2		93.27	3.09	3.31							
Dec	3	92.90	1.15	1.24	-0.94	2		96.32	3.57	3.71							
Nov	6	94.70	4.10	4.33	-0.76	2		97.05	3.61	3.72							
Oct	9	95.49	3.19	3.34	-0.55	2		96.65	2.59	2.68							
Sep	8	96.19	4.86	5.05	0.44	2		96.11	4.23	4.40							

Have we got a trend?



Laboratory: 29584
Cambridge University Hospitals Nhs
Box 217
Cambridge CA
Report period: 03/01/22 - 03/31/22
Comparison area: Worldwide

Laboratory Summary

Condensed

werfen

CONTROL
HemosIL Normal Control ASSAYED

CONTROL LOT
N1108804

REAGENT LOT
N0403055

TEST
PT- RecombiPlasTin

UNIT
seconds

SYSTEM GROUP
ACL TOP Family

SN / MODEL
(14120102) ACL TOP 750 CTS

YOUR CURRENT MONTH STATISTICS								YOUR CUMULATIVE STATISTICS				PEER GROUP STATISTICS							
N	MEAN	1SD	-2SD	+2SD	CV	SDI	CVI	N	MEAN	PSD	CV	LABS	MEAN	PSD	CV	-2SD	+2SD	SD OF MEANS	COMMENTS
60	11.76	0.24	11.28	12.24	2.04	0.00	0.88	390	11.77	0.22	1.88	29	11.76	0.27	2.33	11.21	12.30	0.30	

CONTROL
HemosIL High Abnormal Control ASSAYED

CONTROL LOT
N1209113

REAGENT LOT
N0403055

TEST
PT- RecombiPlasTin

UNIT
seconds

SYSTEM GROUP
ACL TOP Family

SN / MODEL
(14120102) ACL TOP 750 CTS

YOUR CURRENT MONTH STATISTICS								YOUR CUMULATIVE STATISTICS				PEER GROUP STATISTICS							
N	MEAN	1SD	-2SD	+2SD	CV	SDI	CVI	N	MEAN	PSD	CV	LABS	MEAN	PSD	CV	-2SD	+2SD	SD OF MEANS	COMMENTS
65	35.23	1.48	32.27	38.19	4.20	-0.58	1.05	641	35.02	1.23	3.52	94	35.93	1.43	3.99	33.06	38.80	1.20	

Laboratory: 29584
Cambridge University Hospitals Nhs
Box 217
Cambridge CA
Report period: 03/01/22 - 03/31/22
Comparison area: Worldwide

Laboratory Summary

Full

werfen

CONTROL
HemosIL Normal Control ASSAYED

CONTROL LOT
N1108804

REAGENT LOT
N0403055

TEST
PT- RecombiPlasTin

UNIT
seconds

SYSTEM GROUP
ACL TOP Family

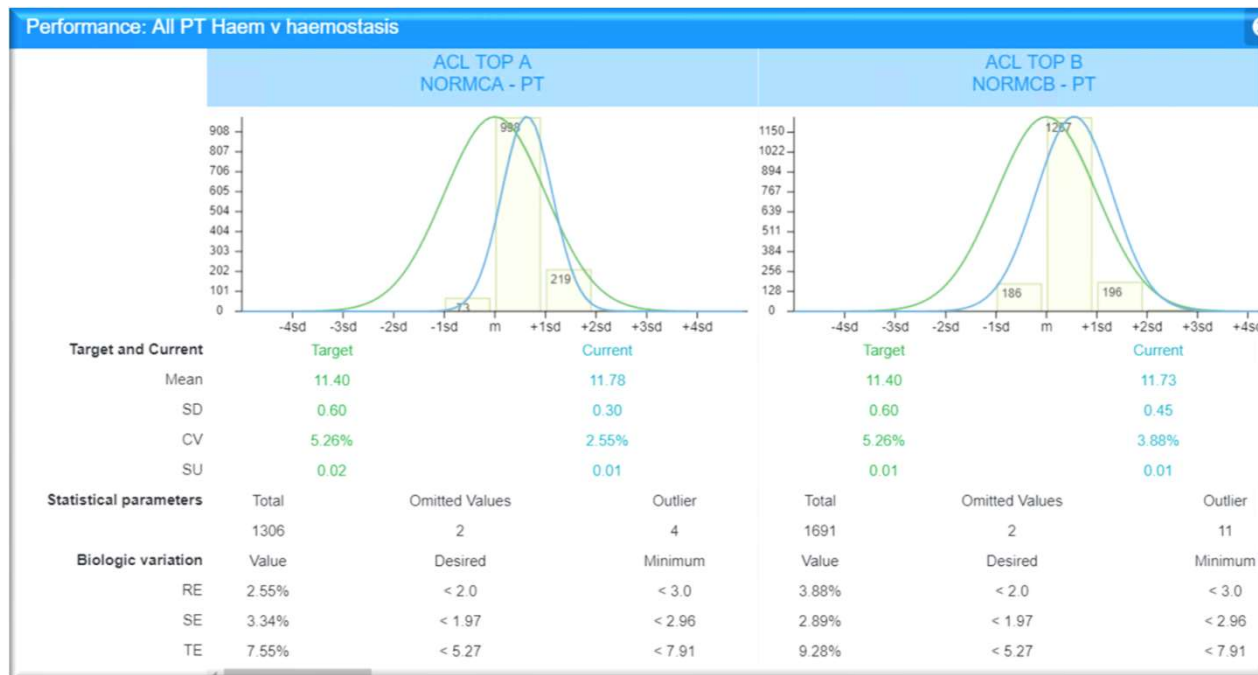
SN / MODEL
(14120102) ACL TOP 750 CTS

MONTH	N	YOUR MEAN	GROUP MEAN	SDI	LABS	YOUR 1SD	GROUP PSD	YOUR CV	GROUP CV	COMMENTS	MEAN		PSD	
											YOUR YTD	GROUP YTD	YOUR YTD	GROUP YTD
Mar	60	11.76	11.76	0.00	29	0.24	0.27	2.04	2.33		11.77	11.89	0.22	0.29
Feb	49	11.88	11.84	0.15	33	0.25	0.30	2.10	2.56					
Jan	54	11.93	11.86	0.17	34	0.23	0.29	1.93	2.47					
Dec	53	11.80	11.87	-0.18	27	0.24	0.28	2.03	2.35					
Nov	58	11.72	11.98	-0.48	32	0.20	0.28	1.71	2.35					
Oct	58	11.69	11.89	-0.38	28	0.18	0.28	1.54	2.39					
Sep	58	11.66	11.97	-0.72	24	0.21	0.27	1.80	2.22					



What does AccuTrack™ 2.0 give us for MU?

- Imprecision individually and pooled across users for comparison
- Bias can be derived
- Even have U of consensus value.....BUT
- Low numbers
 - rotating analysers for comparability – may only be n=2-5
 - No longer describe “long term imprecision”
- Don't over stratify your reports
 - Local is good but only if there are numbers
 - Assays are traceable to the same standard irrespective of reagent lot number
- Country v worldwide v local biases.....



	Analyte	Number of papers	Biological Variation		Desirable specification		
			CV _i	CV _g	I(%)	B(%)	TE(%)
B-	pCO2	1	4.8	5.3	2.4	1.8	5.7
S-	Prolactin	4	23.0	35.0	11.5	10.5	29.4
P-	Proline	1	17.0	104.4	8.5	26.4	40.5
P-	Prolyl endopeptidase	2	16.8	13.9	8.4	5.5	19.3
S-	Properdin factor B	1	9.5	11.2	4.7	3.7	11.5
S-	Prostatic specific antigen (PSA)	3	18.1	72.4	9.1	18.7	33.6
S-	Protein	18	2.75	4.7	1.38	1.36	3.63
S-	Protein, glycosylated	1	0.9	11.6	0.5	2.9	3.7
U-	Protein, output, 24h	2	35.5	23.7	17.8	10.7	40.0
P-	Prothrombin time	2	4.0	6.8	2.0	2.0	5.3
U-	Pyridoxine	1	19.4	23.6	9.7	7.6	23.6

Multiple **Performance** **IQC**

Options

From: 17/04/2021

To: 17/05/2021

Max Bias

☒ 2.8 * (Ref. Instrument SD / Ref. Instrument Mean) * 100

☐ 2.8 * (Σ(CVs) / Number of Instruments)

☐ Value %

Submit

Using AccuTrack™ 2.0 to represent Uncertainty



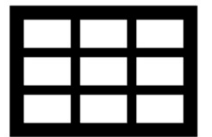
SUMMARISE FOR LAB STAFF



PROVIDE DATA FOR
ACCREDITATION



REDUCE PERIODIC REVIEW
OF EXAMINATIONS



MU Dashboard

Month	Assay	QC	Analyser	Lot_No	N	Mean	1SD	minus_2SD	plus_2SD	CV	SDI	CVI	To_Date_N	To_Date_Mean	To_Date_PSD	To_Date_CV	Labs	GroupMea	Bias_%
30/11/2017	APTT-SynthASil	HemosIL Normal Control	(14120102) ACL TOP 750 CTS	N056305	28	28.840	0.560	27.700	29.960	1.940	0.000	0.947	28	28.840	0.560	1.940	2	28.667	0.6
30/11/2017	Factor VII	HemosIL Normal Control	(15010104) ACL TOP 750 CTS	N0563052	4	81.980	5.160	71.660	92.300	6.294	0.000	1.038	4	81.980	5.160	6.294	2	87.305	-6.1
30/11/2017	PT- RecombiPlasTin	HemosIL High Abnormal	(15010104) ACL TOP 750 CTS	N0278037	25	38.070	1.340	35.390	40.750	3.520	1.024	0.906	25	38.070	1.340	3.520	61	36.625	3.9
30/11/2017	Factor V	HemosIL Special Test Control	(14120102) ACL TOP 750 CTS	N1065945	5	29.480	2.010	25.460	33.500	6.818	0.348	0.998	5	29.480	2.010	6.818	17	28.687	2.8
30/11/2017	APCR-V Ratio	HemosIL FV Leiden Level 1	(14120102) ACL TOP 750 CTS	N1065972	2	2.850	0.180	2.490	3.210	6.316	-0.078	0.925	2	2.850	0.180	6.316	9	2.858	-0.3
30/11/2017	Factor X	HemosIL Special Test Control	(14120102) ACL TOP 750 CTS	N1065945	7	27.230	0.890	25.450	29.010	3.268	-0.273	0.522	7	27.230	0.890	3.268	13	27.952	-2.6
30/11/2017	Factor VIII	HemosIL Special Test Control	(15010104) ACL TOP 750 CTS	N1065945	22	33.150	1.730	29.690	36.610	5.219	0.401	0.620	22	33.150	1.730	5.219	35	31.883	4.0
30/11/2017	Factor II	HemosIL Special Test Control	(14120102) ACL TOP 750 CTS	N1065945	9	30.820	1.470	27.880	33.760	4.770	0.618	1.040	9	30.820	1.470	4.770	10	30.144	2.2
30/11/2017	Factor XIII AG	HemosIL Special Test Control	(15010104) ACL TOP 750 CTS	N1065945	6	19.730	2.140	15.450	24.010	10.846	0.519	0.595	6	19.730	2.140	10.846	3	18.542	6.4
30/11/2017	APTT-SynthASil	HemosIL High Abnormal	(14120102) ACL TOP 750 CTS	N0278037	27	56.600	1.160	54.280	58.920	2.049	-0.871	0.785	27	56.600	1.160	2.049	75	58.379	-3.0
30/11/2017	PT- RecombiPlasTin	HemosIL High Abnormal	(14120102) ACL TOP 750 CTS	N0278037	36	38.090	1.360	35.370	40.810	3.570	1.038	0.918	36	38.090	1.360	3.570	61	36.625	4.0
30/11/2017	Factor XII	HemosIL Special Test Control	(14120102) ACL TOP 750 CTS	N1065945	3	27.800	1.150	25.500	30.100	4.137	-0.507	0.543	3	27.800	1.150	4.137	8	29.289	-5.1
30/11/2017	PT- RecombiPlasTin	HemosIL Normal Control	(15010104) ACL TOP 750 CTS	N0563052	28	11.500	0.170	11.160	11.840	1.478	0.468	0.605	28	11.500	0.170	1.478	6	11.404	0.8
30/11/2017	PT- RecombiPlasTin	HemosIL Normal Control	(14120102) ACL TOP 750 CTS	N0563052	49	11.530	0.240	11.050	12.010	2.082	0.615	0.852	49	11.530	0.240	2.082	6	11.404	1.1
30/11/2017	APTT-SynthASil	HemosIL High Abnormal	(15010104) ACL TOP 750 CTS	N0278037	26	56.010	0.940	54.130	57.890	1.678	-1.160	0.643	26	56.010	0.940	1.678	75	58.379	-4.1
30/11/2017	APTT-SynthASil	HemosIL Normal Control	(14120102) ACL TOP 750 CTS	N0563052	28	28.840	0.560	27.720	29.960	1.942	-0.763	0.845	28	28.840	0.560	1.942	6	29.368	-1.8
30/11/2017	Factor XIII AG	HemosIL Special Test Control	(14120102) ACL TOP 750 CTS	N1065945	3	20.270	2.020	16.230	24.310	9.965	0.756	0.547	3	20.270	2.020	9.965	3	18.542	9.3
30/11/2017	Factor XI	HemosIL Special Test Control	(14120102) ACL TOP 750 CTS	N1065945	14	28.860	2.440	23.980	33.740	8.455	0.776	1.225	14	28.860	2.440	8.455	11	27.364	5.5
30/11/2017	APTT-SynthASil	HemosIL High Abnormal	(15010104) ACL TOP 750 CTS	N0278037	26	56.010	0.940	54.130	57.890	1.678	-0.057	0.286	26	56.010	0.940	1.678	4	56.195	-0.3
30/11/2017	Factor XIII AG	HemosIL Normal Control	(15010104) ACL TOP 750 CTS	N0563052	5	57.880	5.200	47.480	68.280	8.984	0.000	1.160	5	57.880	5.200	8.984	2	58.214	-0.6
30/11/2017	Protein C	HemosIL Normal Control	(15010104) ACL TOP 750 CTS	N0563052	10	104.300	2.060	100.180	108.420	1.975	0.000	1.023	10	104.300	2.060	1.975	2	104.571	-0.3
30/11/2017	Factor IX	HemosIL Special Test Control	(15010104) ACL TOP 750 CTS	N1065945	19	33.390	2.000	29.390	37.390	5.990	1.399	0.676	19	33.390	2.000	5.990	17	30.664	8.9
30/11/2017	Factor VIII	HemosIL Special Test Control	(14120102) ACL TOP 750 CTS	N1065945	11	34.780	2.160	30.460	39.100	6.210	0.918	0.738	11	34.780	2.160	6.210	35	31.883	9.1
30/11/2017	Protein C	HemosIL Special Test Control	(14120102) ACL TOP 750 CTS	N1065945	3	26.000	0.000	26.000	26.000	2.000	0.832	0.000	3	26.000	0.000	0.000	17	24.903	4.4
30/11/2017	Factor II	HemosIL Normal Control	(14120102) ACL TOP 750 CTS	N0563052	7	97.700	1.770	94.160	101.240	1.812	0.000	0.714	7	97.700	1.770	1.812	2	97.200	0.5
30/11/2017	Factor XIII AG	HemosIL Normal Control	(14120102) ACL TOP 750 CTS	N0563052	3	58.770	2.630	53.510	64.030	4.475	0.000	0.578	3	58.770	2.630	4.475	2	58.214	1.0
30/11/2017	APTT-SynthASil	HemosIL High Abnormal	(14120102) ACL TOP 750 CTS	N0278037	27	56.600	1.160	54.280	58.920	2.049	0.125	0.349	27	56.600	1.160	2.049	4	56.195	0.7
30/11/2017	Factor IX	HemosIL Normal Control	(15010104) ACL TOP 750 CTS	N0563052	19	105.090	6.020	93.050	117.130	5.728	0.000	0.453	19	105.090	6.020	5.728	2	101.811	3.2
30/11/2017	APCR-V Ratio	HemosIL FV Leiden Level 2	(15010104) ACL TOP 750 CTS	N1065787	6	1.680	0.040	1.600	1.760	2.381	0.278	0.583	6	1.680	0.040	2.381	8	1.675	0.3
30/11/2017	Factor II	HemosIL Special Test Control	(15010104) ACL TOP 750 CTS	N1065945	2	28.300	1.700	24.900	31.700	6.007	-1.687	1.310	2	28.300	1.700	6.007	10	30.144	-6.1
30/11/2017	Factor V	HemosIL Normal Control	(14120102) ACL TOP 750 CTS	N0563052	7	98.200	4.780	88.640	107.760	4.868	0.000	1.180	7	98.200	4.780	4.868	2	99.247	-1.1
30/11/2017	APTT-SynthASil	HemosIL Normal Control	(15010104) ACL TOP 750 CTS	N0563052	33	28.520	0.610	27.300	29.740	2.139	-1.225	0.963	33	28.520	0.610	2.139	6	29.368	-2.9
30/11/2017	Factor VII	HemosIL Special Test Control	(14120102) ACL TOP 750 CTS	N1065945	8	25.860	1.260	23.340	28.380	4.872	0.745	0.815	8	25.860	1.260	4.872	17	24.225	6.7
30/11/2017	Factor XII	HemosIL Normal Control	(15010104) ACL TOP 750 CTS	N0563052	10	94.170	4.300	85.570	102.770	4.566	0.000	0.923	10	94.170	4.300	4.566	2	92.947	1.3
30/11/2017	VWF AG	HemosIL Normal Control	(15010104) ACL TOP 750 CTS	N0563052	15	121.850	2.280	117.290	126.410	1.871	0.000	0.986	15	121.850	2.280	1.871	2	122.734	-0.7
30/11/2017	Factor X	HemosIL Special Test Control	(15010104) ACL TOP 750 CTS	N1065945	3	25.530	1.850	21.830	29.230	7.246	-0.915	1.158	3	25.530	1.850	7.246	13	27.952	-8.7
30/11/2017	VWF AG	HemosIL Special Test Control	(15010104) ACL TOP 750 CTS	N1065945	15	40.170	1.110	37.950	42.390	2.763	0.135	0.705	15	40.170	1.110	2.763	18	39.969	0.5
30/11/2017	Protein C	HemosIL Normal Control	(14120102) ACL TOP 750 CTS	N0563052	4	105.250	1.890	101.470	109.030	1.796	0.000	0.930	4	105.250	1.890	1.796	2	104.571	0.6
30/11/2017	Factor VII	HemosIL Special Test Control	(15010104) ACL TOP 750 CTS	N1065945	5	22.400	2.040	18.320	26.480	9.107	-0.831	1.523	5	22.400	2.040	9.107	17	24.225	-7.5
30/11/2017	Antithrombin	HemosIL Special Test Control	(15010104) ACL TOP 750 CTS	N1065945	18	25.890	2.560	20.770	31.010	9.888	1.405	0.650	18	25.890	2.560	9.888	33	22.045	17.4

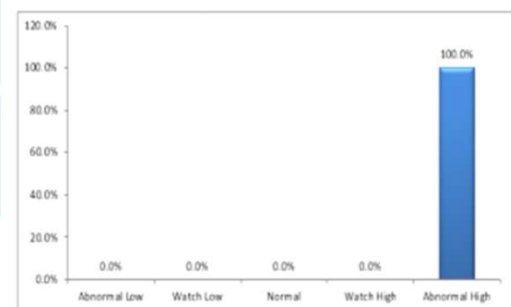
Specialist Haemostasis, Haematology and Papworth Blood Sciences Measurement Uncertainty dashboard

Assay	Anti-Xa	APCR-V	APTT-SP	APTT-SynthASil	dRVVT	Factor II	Factor IX	Factor V	Factor VII
Anthrithrombin	Factor X	Factor XI	Factor XII	Factor XIII AG	Fibrinogen-GFA	Free Protein S	Protein C	PT-RecombiPlasTin	Thrombin Time (S/mL)
VWF AG	ANTI-XA IU/mL	APCR-V Ratio	APCV-1	APCV-2	APTT	APTT Seconds	APTT SP	APTT SS	AT Liquid

Month
31/07/2021
31/08/2021
30/09/2021
31/10/2021
30/11/2021
31/12/2021
31/01/2022
31/02/2022
31/03/2022
31/04/2022
31/05/2022
31/06/2022
31/07/2022
(blank)

Analysed
(14120102) A...
(15010104) A...
(15090126) ...
(15090177)
Lab
SH
Haem
Papworth

Assay	PT-RecombiPlasTin	Calibrated?	N	
Lab	(All)			
Row Labels	Sum of N	Average of M	Average of B	Average of Bias
HemosIL High Abnorm	700	35.13	3.26	-0.24
31/08/2021	106	34.76	2.72	
30/09/2021	111	34.83	2.81	
31/10/2021	112	35.05	2.90	1.38
30/11/2021	115	35.02	3.15	-1.44
31/12/2021	112	35.35	3.82	-0.98
31/01/2022	144	35.75	4.15	0.08
HemosIL Normal Contr	648	11.69	1.83	-0.60
31/08/2021	106	11.48	1.70	
30/09/2021	110	11.61	1.81	
31/10/2021	107	11.67	1.67	0.28
30/11/2021	108	11.71	1.71	-2.25
31/12/2021	105	11.75	2.09	-1.01
31/01/2022	112	11.93	2.02	0.59
Grand Total	1348	23.41	2.54	-0.42



Assay	PT-RecombiPlasTin
QC Level 1	HemosIL High Abnormal
n	700
CV (U ₉₅)	3.26%
Mean Bias	-0.24
QC Level 2	HemosIL Normal Control
n	648
CV (U ₉₅)	1.83%
Mean Bias	-0.60
QC Levels	2
Denominator	1346
Imprecision (Pooled SD)	2.7%
CV _{avg} (k=1.96)	5.2%
test (unequal variances of 6 month data CV)	
p=	0.000 significant

U _{calibrator assigned value} *	3.00%
U _{traceability}	0.002%
Traceability Hierarchy	WHO S81612
U _{calibration}	0
Bias	-0.42%
Bias sig	not significant
U _{lim}	Not included
MU limit	20.00%
Overall MU	4.07%
MU normal level	5.46%
MU pathological level	3.95%
Traceability Hierarchy	
WHO	0.002%
House standard	0.07%
Arbitrary Unit	%
Production item	5%

CV	Mean	CV*1.96	Slope	Intercept
2.72	34.76	5.32	0.120	2.166
2.81	34.83	5.51		
2.90	35.05	5.67		
3.15	35.02	6.16		
3.82	35.35	7.49		
4.15	35.75	8.12		
1.70	11.48	3.32		
1.81	11.61	3.55		
1.67	11.67	3.27		
1.71	11.71	3.35		
2.09	11.75	4.09		
2.02	11.93	3.95		
	Mean (6)	6.38		

Clinically significant action points - extrapolated by linear modelling of the above calculation

PT-RecombiPlasTin

Abnormal Low
Watch Low
Normal
Watch High
Abnormal High

0.0%
0.0%
0.0%
0.0%
100.0%

Reference range interpretation - insert factors as UoL

Patient result

73.00

Ref Range

69.18 to 76.82

MU Ref range

10.05 to 11.15

Abnormal

Watch

Normal

Watch

Abnormal

12.13 to 13.47

Date Assessed

Assessed by:

10 +/- 0.3
13 +/- 0.49
16 +/- 0.65
19 +/- 0.85
25 +/- 1.29
35 +/- 2.23
50 +/- 4.09

CV₁ 2.60%

CV₂ 4.60%

aCV Monitoring 1.30%

aCV Diagnostic 3.00%

Analytical Bias 1.30%

TEa 3.40%

Analytical Critical Difference

A difference between 2 results of 0.07 is required to be analytically significantly different with 95% confidence

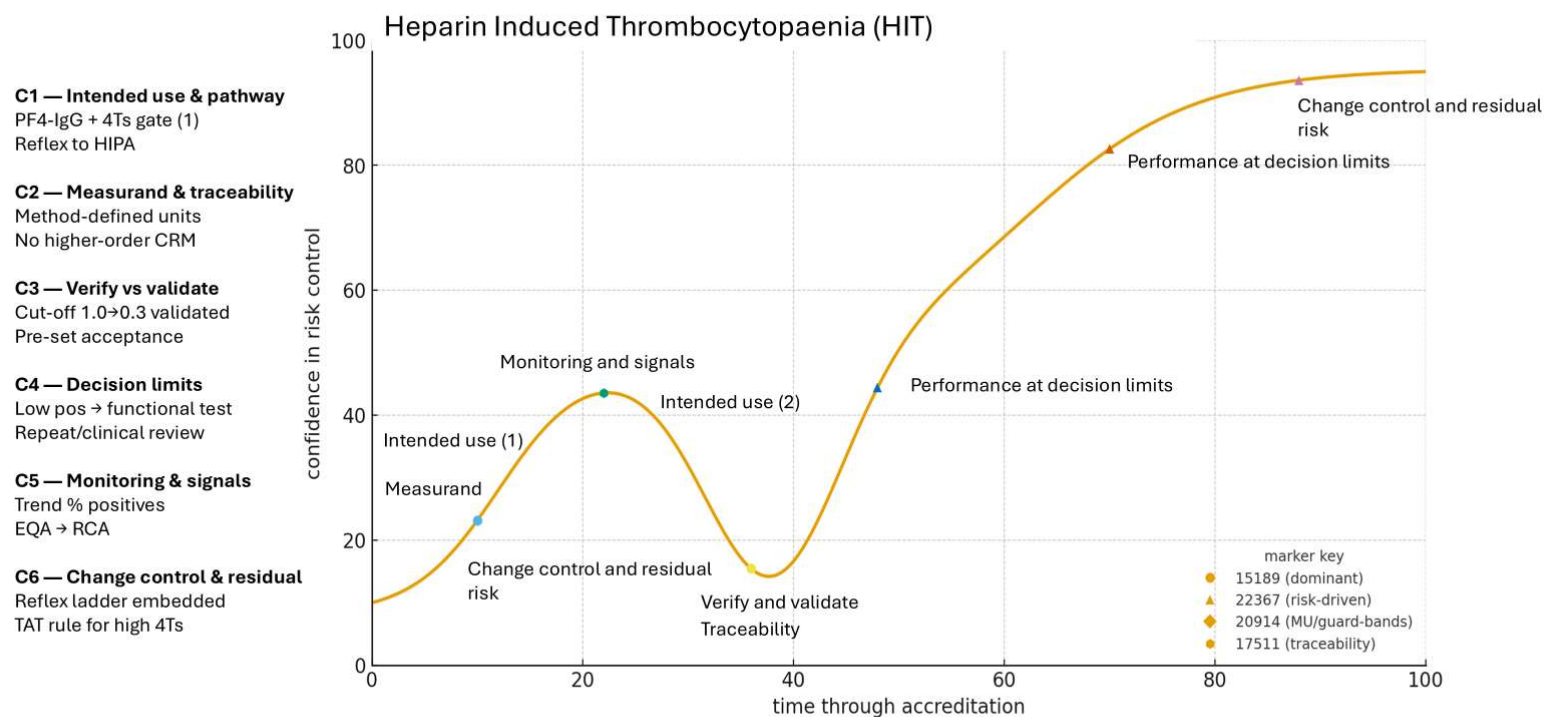
In the above patient a result within the range below is not analytically statistically significantly different from the result entered

72.93 to 73.07

Sequential results

Incorporating biological variation two sequential samples must differ by 1.9 to be significantly different

What about semi quantitative tests?





Bayesian Approach



**Normal Distribution
Approach**



**Information-Theoretic
Approach**

$$P(A|Pos) = \frac{P(Pos|A) \times P(A)}{P(Pos)}$$
$$= \frac{P(Pos|A) \times P(A)}{P(Pos|A) \times P(A) + P(Pos|not A) \times P(not A)}$$

$$P(A|Pos) = \frac{sensitivity \times prevalence}{sensitivity \times prevalence + (1 - specificity) \times (1 - prevalence)}$$

= Positive predictive value

$$Positive\ likelihood\ ratio = \frac{P(Pos | A)}{P(Pos | not A)} = \frac{sensitivity}{1 - specificity}$$

$$Negative\ likelihood\ ratio = \frac{P(Neg | not A)}{P(Neg | A)} = \frac{specificity}{1 - sensitivity}$$



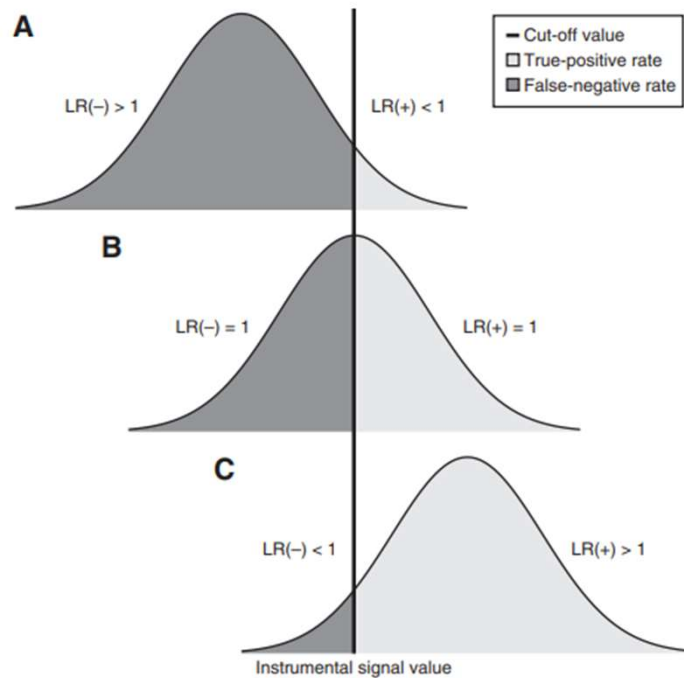
Bayesian Approach



Normal Distribution Approach

0/1

Information-Theoretic Approach



$$f(x | \mu, \sigma^2) = \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{(x-\mu)^2}{2\sigma^2}}$$

$$\text{True-positive rate} = \Pr[r_{\text{cut-off}} \leq X \leq \infty] = \int_{r_{\text{cut-off}}}^{\infty} f(x | \mu, \sigma^2) dx$$

False-negative rate

$$= \Pr[-\infty \leq X \leq r_{\text{cut-off}}] = \int_{-\infty}^{r_{\text{cut-off}}} f(x | \mu, \sigma^2) dx$$



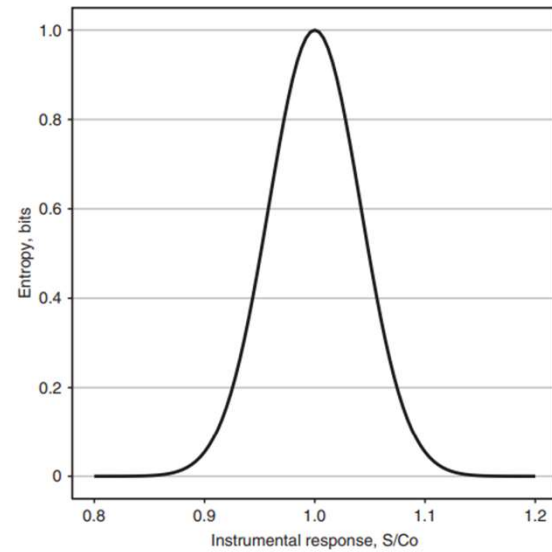
Bayesian Approach



**Normal Distribution
Approach**

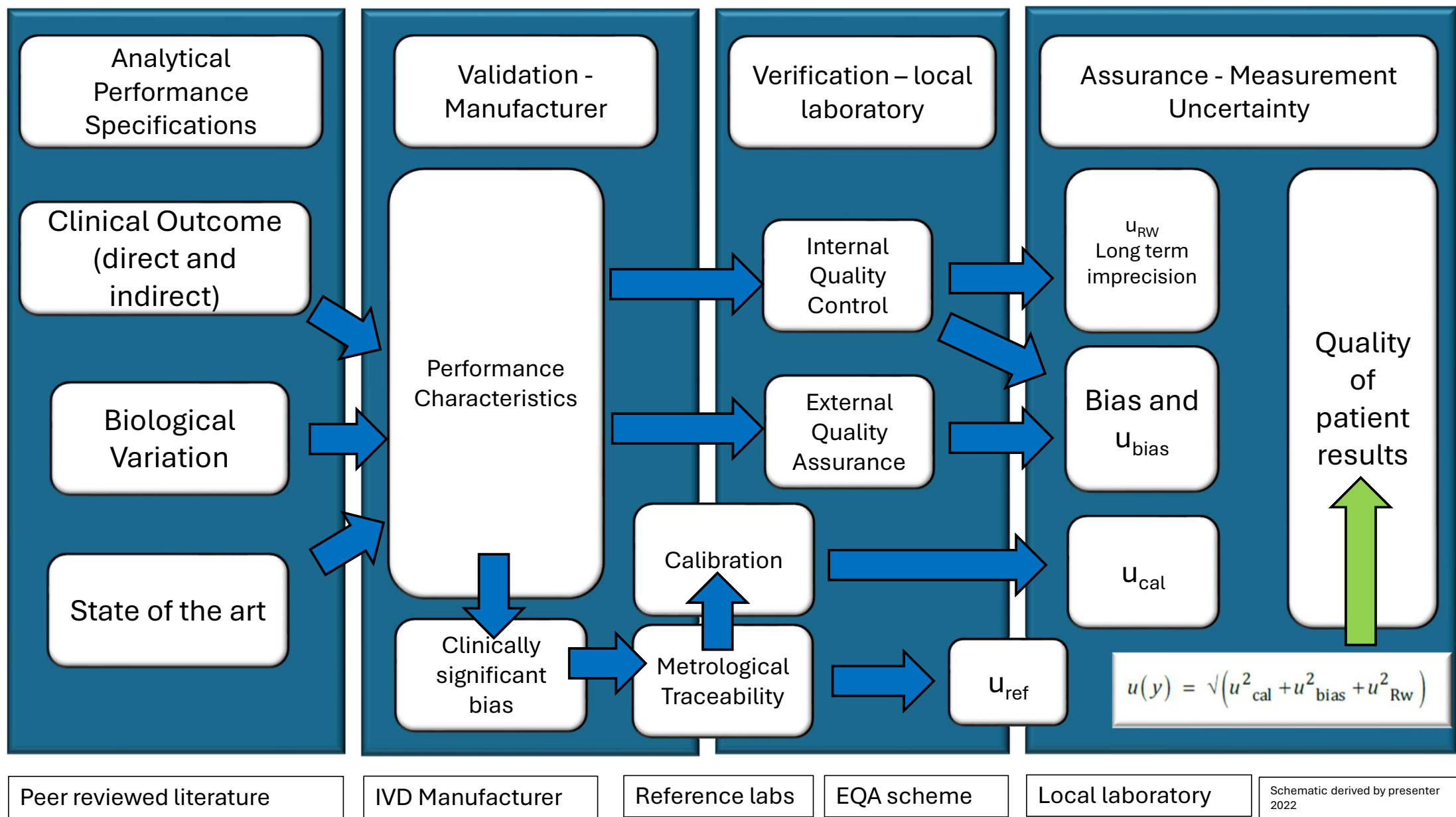
0|1

**Information-Theoretic
Approach**



$$S = -p \times \log_2(p) - (1-p) \times \log_2(1-p)$$

Approach	What it Measures	Everyday Meaning
Bayesian	Probability that the result is correct, based on known test performance (sensitivity, specificity, prevalence).	“How likely are we right?”
Normal Distribution	Certainty based on how far the test result lies from the cut-off value, given the signal’s variability.	“How close are we to the grey zone?”
Information Theory	The overall amount of uncertainty (entropy) associated with the result’s probability distribution.	“How much useful information does the test actually give?”



Take home messages ¹

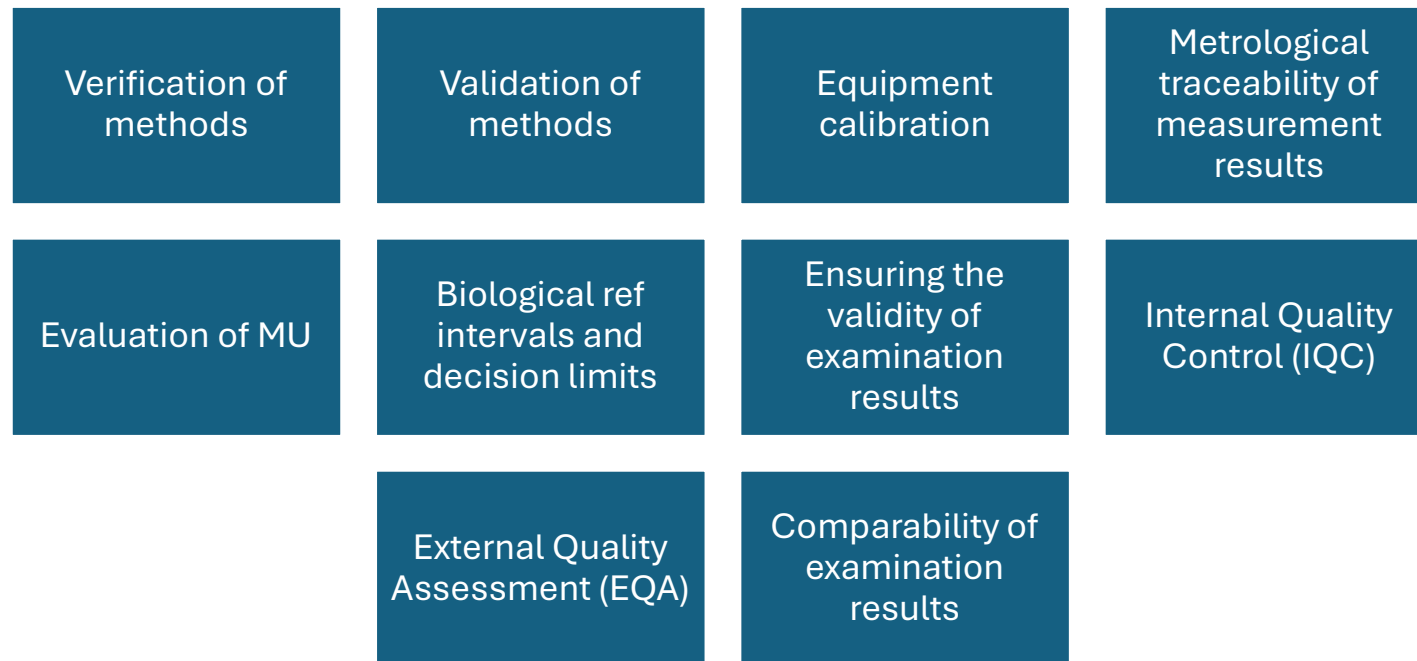
$$u(y) = \sqrt{u_{\text{cal}}^2 + u_{\text{bias}}^2 + u_{\text{RW}}^2}$$

- The maths are simpler
- Analytical Performance Specifications (APS) run through the whole process
- Metrological Traceability is indispensable in assessments
 - u_{cal}
 - u_{ref}
- V&V – accept as clinically acceptable (against APS) -> interim estimate
- Update when u_{RW} data is available and monitor -> working MU
- Interpretation is again related to APS
- No numerical result? – assess the steps that lead to a result
- Risk based exclusion of MU – if appropriate

MU – Measurement Uncertainty, u_{RW} – Uncertainty of the random variation within laboratory/within laboratory precision, V&V – Validation and Verification, APS – Analytical Performance Specifications
 u_{cal} – uncertainty of the calibrator assigned value, u_{ref} – uncertainty of the assigned value of the reference material

Presenters opinion

MU is not relevant.....



Thanks for your attention

- I am happy to take any questions
- stephenmacdonald1@nhs.net