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European Committee for External Quality Assurance
Programmes in Laboratory Medicine

RESULTS OF THE INTERNATIONAL INR PROJECT

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Working Group on Haemostasis
International INR Project

- **Project was performed in 2008**
- **618 participants from 10 different European countries**
- **Set of 4 different samples**
- **INR measurement with regular method**
- **Standardized report form + questionnaire**

Project Group: Karin Kynde (DEKS, Denmark)
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Advisor: Ton v.d. Besselaar (The Netherlands)

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The scope of this study was to get an overview of the analytical quality of INR measurements in European countries, and to see if the INR level is the same around laboratories in Europe or if there are:

- Differences between a single plasma portion and a pool of several plasmas.
- Differences between the assays types (Quick vs. Owren).
- Differences between same types of reagents from different manufactures.
- Differences between countries.
- Differences between the different ways of calibration (kind of calibrators, local vs. manufacturers calibration).

Each laboratory has received a set of 4 different plasmas, two samples with an INR of 2.0 - 2.5 and two samples with an INR level of 3.0 - 3.5 INR.

- Sample 1: Single plasma, low INR range**
- Sample 2: Plasma pool, low INR range**
- Sample 3: Single plasma, high INR range**
- Sample 4: Plasma pool, high INR range**

Plasma pools were prepared from at least 10 different donors. The sample were prepared under supervision of Tim Woods at the UKNEQAS, Sheffield, United Kingdom.

RESULTS

All results for each sample were pooled together and the mean and standard deviation were calculated. Each result deviating more than 3 times the standard deviation was indentified as an outlier.

The acceptance limits for each of the sample is:

Sample 1: 1.56 – 2.70

Sample 2: 1.84 – 3.28

Sample 3: 1.91 – 4.37

Sample 4: 2.35 – 4.21

OVERALL

	Sample 1	Sample 2	Sample 3	Sample 4
Number	605	603	599	602
Mean	2.12	2.55	3.09	3.27
Median	2.11	2.55	3.07	3.27
Std. Deviation	0.15	0.19	0.27	0.26
Minimum	1.59	1.87	2.01	2.40
Maximum	2.69	3.26	4.32	4.20
CV (%)	7.1	7.5	8.7	8.0

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QUICK VS OWREN

Test	Description
Quick	<ul style="list-style-type: none">• Undiluted plasma• 1 vol. plasma + 1 vol. thromboplastin + 1 vol. Calciumchloride• Final plasma dilution: 1 + 2• Dependent on Factor II, VII,X and of Factor V and Fibrinogen
Owren	<ul style="list-style-type: none">• Plasma dilution (1+6) with buffer containing citrate• Combined reagent: thromboplastin, Factor V, Fibrinogen, Calciumchloride• 1 vol. diluted plasma + 2 vol. combined reagent• Final plasma dilution: 1+20

QUICK VS OWREN

QUICK	OWREN
N = 363	N = 245
Belgium Croatia France Germany Romania Netherlands	Denmark Finland Norway Sweden Netherlands

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QUICK	OWREN
N = 363	N = 245
Simplastin Excel S (BioMerieux) Simplastin HTF (BioMerieux) Simplastin LS (BioMerieux) Innovin (Dade Behring) Thromborel S (Dade Behring) PT-FIB-HS (IL) PT-FIB-RECOMB (IL) Recombiplastin (IL) Recombiplastin 2G (IL) Thromboplastin DS (PH) Neoplastin CI (Stago) Neoplastin CI Plus (Stago) Neoplastin R (Stago) Technoplastin HS (Technoclone)	Owrens PT (Medirox) Nycotest PT (Nycomed) Thrombotest PT (Nycomed) SPA 20 / 50 (Stago) Hepato Quick (Stago)

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	Sample 1	Sample 2	Sample 3	Sample 4
OWREN				
Number	243	240	245	245
Mean	2.05	2.54	2.99	3.23
CV (%)	5.8	6.7	7.0	7.4
QUICK				
Number	362	363	354	357
Mean	2.17	2.55	3.16	3.29
CV (%)	6.9	8.2	8.9	8.5
P-Value	< 0.01	N.S.	< 0.01	< 0.01

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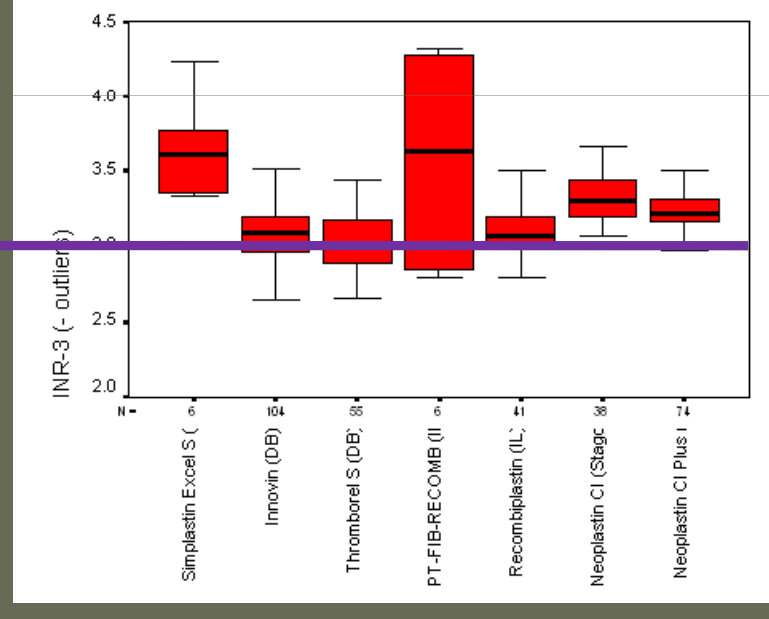
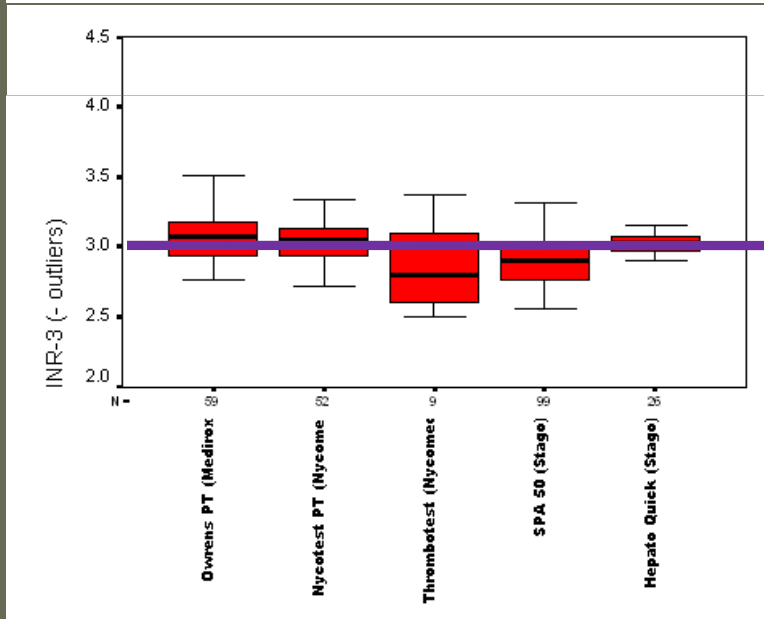
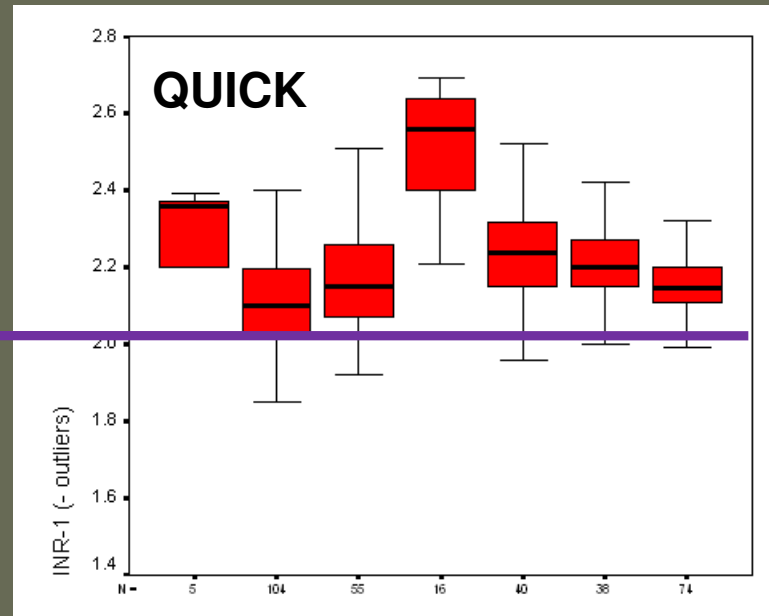
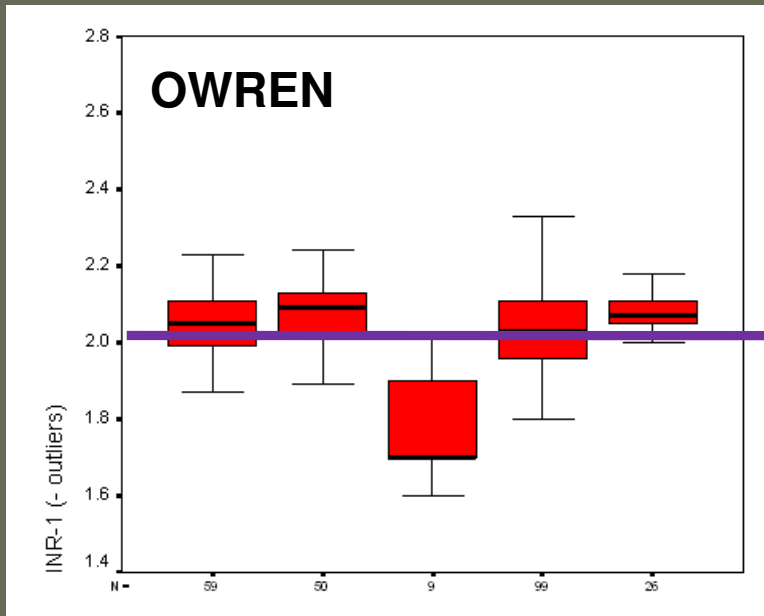
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REAGENTS

QUICK		OWREN	
Simplastin Excel S (BioMerieux)	6	Owrens PT (Medirox)	59
Simplastin HTF (BioMerieux)	2	Nycotest PT (Nycomed)	52
Simplastin LS (BioMerieux)	1	Thrombotest PT (Nycomed)	9
Innovin (Dade Behring)	104	SPA 20 / 50 (Stago)	100
Thromborel S (Dade Behring)	55	Hepato Quick (Stago)	26
PT-FIB-HS (IL)	3		
PT-FIB-RECOMB (IL)	22		
Recombiplastin (IL)	41		
Recombiplastin 2G (IL)	2		
Thromboplastin DS (PH)	3		
Neoplastin CI (Stago)	39		
Neoplastin CI Plus (Stago)	74		
Neoplastin R (Stago)	10		
Technoplastin HS (Technoclone)	1		

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OWREN REAGENTS

	Sample 1	Sample 2	Sample 3	Sample 4
<u>Owrens PT</u> (n=59)				
Mean	2.05	2.56	3.06	3.26
<u>Nycotest PT</u> (n=52)				
Mean	2.10	2.57	3.08	3.27
<u>Thrombotest</u> (n=9)				
Mean	1.77	2.24	2.86	2.80
<u>SPA 20 / 50</u> (n=100)				
Mean	2.04	2.54	2.90	3.22
<u>Hepato Quick</u> (n=26)				
Mean	2.08	2.60	3.03	3.30

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OWREN REAGENTS

	Sample 1	Sample 2	Sample 3	Sample 4
<u>Owrens PT</u> (n=59)				
CV (%)	4.0	5.1	4.9	5.5
<u>Nycotest PT</u> (n=52)				
CV (%)	5.7	7.8	8.1	7.3
<u>Thrombotest</u> (n=9)				
CV (%)	8.5	9.4	11.2	11.4
<u>SPA 20 / 50</u> (n=100)				
CV (%)	5.9	6.7	6.9	7.8
<u>Hepato Quick</u> (n=26)				
CV (%)	2.4	2.8	2.4	2.7

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QUICK REAGENTS

	Sample 1	Sample 2	Sample 3	Sample 4
	Mean	Mean	Mean	Mean
Innovin (n=104)	2.11	2.39	3.09	3.11
Thromborel S (n=55)	2.16	2.55	3.03	3.11
PT-FIB-RECOMB (n=22)	2.47	2.96	3.59	3.80
Recombiplastin (n=41)	2.25	2.65	3.12	3.49
Neoplastin CI (n=39)	2.21	2.58	3.30	3.29
Neoplastin CI Plus (n=74)	2.15	2.62	3.25	3.33
Neoplastin R (n=10)	2.20	2.61	3.22	3.48

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QUICK REAGENTS

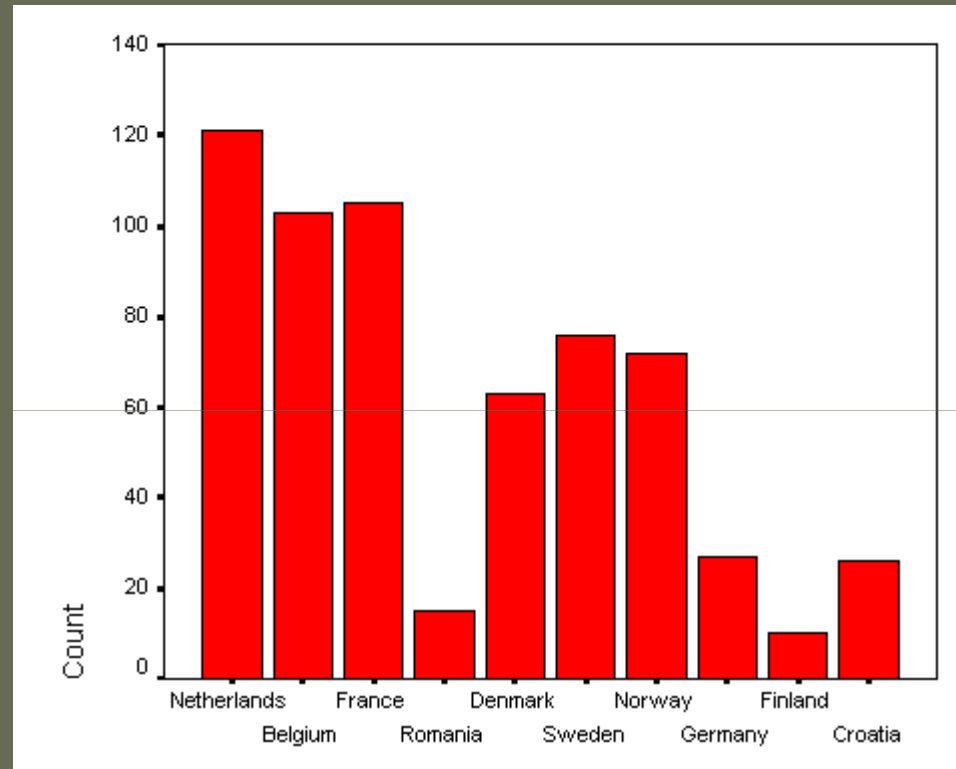
	Sample 1	Sample 2	Sample 3	Sample 4
	CV (%)	CV (%)	CV (%)	CV (%)
Innovin (n=104)	5.2	5.0	6.5	6.1
Thromborel S (n=55)	6.5	6.7	6.9	7.3
PT-FIB-RECOMB (n=22)	9.3	9.8	21.7	11.3
Recombiplastin (n=41)	6.2	6.4	7.4	7.4
Neoplastin CI (n=39)	4.3	5.4	4.8	4.6
Neoplastin CI Plus (n=74)	3.4	3.8	4.9	4.5
Neoplastin R (n=10)	5.0	6.1	7.8	4.6

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COUNTRIES

Netherlands	121
Belgium	103
France	105
Romania	15
Denmark	63
Sweden	76
Norway	72
Germany	27
Finland	10
Croatia	26



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	Sample 1	Sample 2	Sample 3	Sample 4
	Mean	Mean	Mean	Mean
Netherlands	2.15	2.53	3.09	3.27
Belgium	2.17	2.56	3.19	3.32
France	2.19	2.60	3.23	3.33
Romania	2.06	2.39	3.01	3.08
Germany	2.17	2.52	3.11	3.25
Croatia	2.20	2.53	3.09	3.28
Denmark	2.09	2.59	3.05	3.32
Sweden	2.03	2.53	2.98	3.20
Norway	2.03	2.50	2.92	3.18
Finland	2.00	2.54	3.11	3.25
ANOVA	P < 0.001	P = 0.018	P < 0.001	P = 0.001

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	Sample 1	Sample 2	Sample 3	Sample 4
	CV (%)	CV (%)	CV (%)	CV (%)
Netherlands	7.9	9.5	8.1	9.5
Belgium	6.5	7.8	8.8	8.4
France	4.3	5.0	5.3	4.8
Romania	12.1	10.9	21.3	13.0
Germany	6.9	7.9	7.1	8.3
Croatia	5.5	6.3	7.4	6.7
Denmark	6.2	7.3	8.2	7.8
Sweden	4.4	5.1	5.7	5.6
Norway	7.4	8.8	8.2	9.1
Finland	6.0	4.3	4.5	5.2

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	Innovin	Thromborel S	PT-FIB-RECOMB	Recombiplastin	Neoplastin CI	Neoplastin CI Plus	Neoplastin R	Hepato Quick	Owrens PT	Nycotest	Thrombotest	SPA 20 / 50
Netherlands	55	5	12	9	-	2	2	25	-	-	-	-
Belgium	29	8	3	18	-	28	8	-	-	-	-	-
France	3	15	1	5	38	41	-	-	-	-	-	-
Romania	-	5	-	1	-	-	-	-	-	-	-	-
Germany	6	10	-	4	-	3	-	1	-	-	-	-
Croatia	11	12	-	3	-	-	-	-	-	-	-	-
Denmark	-	-	-	-	-	-	-	-	11	19	-	30
Sweden	-	-	-	-	-	-	-	-	41	13	-	21
Norway	-	-	-	-	-	-	-	-	6	15	5	46
Finland	-	-	-	-	-	-	-	-	1	3	4	2

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	Sample 1	Sample 2	Sample 3	Sample 4
Innovin				
Netherlands	2.08 (3.7)	2.37 (4.6)	3.06 (5.6)	3.08 (5.2)
Belgium	2.11 (5.7)	2.37 (5.5)	3.09 (7.1)	3.11 (6.4)
Thromborel S				
France	2.20 (6.4)	2.58 (5.4)	3.09 (5.5)	3.36 (6.3)
Germany	2.16 (8.3)	2.53 (10.7)	3.09 (9.1)	3.28 (10.1)
Croatia	2.17 (6.5)	2.74 (7.7)	3.03 (5.9)	3.27 (7.6)
Neoplastin CI Plus				
Belgium	2.13 (3.5)	2.60 (3.3)	3.24 (6.2)	3.31 (4.5)
France	2.16 (2.9)	2.63 (3.7)	3.25 (4.0)	3.35 (4.2)

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	Sample 1	Sample 2	Sample 3	Sample 4
Owrens PT				
Sweden	2.06 (3.8)	2.56 (5.1)	3.06 (4.9)	3.25 (5.5)
Denmark	2.02 (3.4)	2.54 (5.5)	2.98 (5.0)	3.22 (3.7)
Nycotest PT				
Sweden	2.04 (3.3)	2.56 (5.1)	2.96 (3.3)	3.19 (4.1)
Denmark	2.14 (7.0)	2.54 (8.3)	3.10 (10.3)	3.26 (8.6)
Norway	2.11 (4.3)	2.60 (9.6)	3.12 (7.4)	3.36 (7.7)
SPA 20/50				
Sweden	1.98 (5.1)	2.45 (5.3)	2.82 (4.3)	3.09 (5.5)
Denmark	2.08 (5.8)	2.63 (6.8)	3.03 (6.9)	3.39 (7.7)
Norway	2.03 (5.9)	2.50 (6.4)	2.85 (6.7)	3.16 (6.3)

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	Sample 1	Sample 2	Sample 3	Sample 4
Reagents				
Low	1.59	1.87	2.01	2.80
High	2.49	2.96	4.04	3.80
Countries				
Low	2.00	2.39	2.92	3.08
High	2.20	2.60	3.23	3.33

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LOCAL CALIBRATION

- **Overall: 55% performed local calibration**
- **Owren: 98% local calibration**
- **Quick: 31% local calibration**

	Sample 1	Sample 2	Sample 3	Sample 4
NO				
Number	264	266	256	261
Mean	2.18	2.58	3.17	3.32
CV (%)	7.8	8.5	9.5	9.0
YES				
Number	333	329	335	333
Mean	2.08	2.51	3.03	3.22
CV (%)	5.8	6.8	7.6	6.8
P-Value	< 0.001	< 0.001	< 0.001	< 0.001

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YES	Sample 1	Sample 2	Sample 3	Sample 4
OWREN				
Number	215	211	216	216
Mean	2.05	2.55	2.99	3.25
CV (%)	5.4	6.3	7.0	6.8
QUICK				
Number	118	118	119	117
Mean	2.13	2.45	3.09	3.18
CV (%)	6.1	6.5	7.4	6.9
P-Value	< 0.001	< 0.001	< 0.001	< 0.001

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QUICK	Sample 1	Sample 2	Sample 3	Sample 4
NO				
Number	237	238	228	233
Mean	2.20	2.60	3.20	3.34
CV (%)	7.3	8.1	9.1	8.7
YES				
Number	118	118	119	117
Mean	2.13	2.45	3.09	3.18
CV (%)	6.1	6.5	7.4	6.9
P-Value	< 0.001	< 0.001	< 0.001	< 0.001

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COUNTRY	YES	NO
Belgium	25	75
Croatia	38	62
France	23	77
Germany	24	76
Romania	14	86
Netherlands	46	54
Denmark	98	2
Finland	100	0
Norway	93	7
Sweden	100	0

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BELGIUM	Sample 1	Sample 2	Sample 3	Sample 4
NO				
Number	75	75	74	72
Mean	2.20	2.61	3.23	3.38
CV (%)	6.4	6.5	8.7	7.7
YES				
Number	25	25	26	24
Mean	2.10	2.39	3.08	3.13
CV (%)	6.7	7.1	8.8	8.0

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NL	Sample 1	Sample 2	Sample 3	Sample 4
NO				
Number	59	59	50	57
Mean	2.21	2.64	3.12	3.39
CV (%)	9.5	10.2	10.6	10.6
YES				
Number	54	54	54	54
Mean	2.09	2.41	3.05	3.13
CV (%)	4.3	6.2	5.2	5.8

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	Sample 1	Sample 2	Sample 3	Sample 4
Provider				
DEKS (59)	2.09 (6.2)	2.61 (5.7)	3.06 (7.8)	3.34 (6.6)
EQUALIS (142)	2.04 (4.9)	2.53 (6.3)	2.96 (6.8)	3.21 (6.5)
RELAC (7)	2.16 (4.0)	2.53 (5.9)	3.17 (2.1)	3.29 (4.9)
Dade Behring (79)	2.10 (5.7)	2.40 (6.3)	3.05 (6.2)	3.13 (6.7)
Technoclone (5)	2.14 (5.1)	2.51 (4.0)	3.00 (5.3)	3.20 (4.4)
Bioclin (8)	2.04 (4.7)	2.57 (3.8)	3.09 (4.9)	3.29 (4.9)

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CONCLUSIONS

1. There are no systematic differences in the between-laboratory variation for a single-plasma sample and a pooled-plasma sample when all results for a plasma are evaluated together.
2. The between-laboratory variation in the Owren-group is less than those in the Quick-group (on average: 6.7% vs 8.1%, respectively).
3. Differences in the mean INR value between the Owren- and Quick group are relatively small (< 0.20).
4. The between-laboratory variation of participants who applied local INR calibration (CV: 6.7%) was lower than the variation between participants who did not (CV: 8.7%).

CONCLUSIONS

5. After local calibration the between-laboratory variation between the Owren and Quick-groups is quite similar (on average: 6.4% vs. 6.7%, respectively).
6. Variation in the average INR results between reagents is higher for single donor plasmas (samples 1 and 3) than for pooled plasmas (samples 2 and 4).
7. Clinically significant differences (difference in INR > 0.5) in INR results were observed between different reagents.
8. There are no clinically significant differences between the mean INR values of countries.

Thank you for your attention

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