Table 1. Baseline characteristics and rates of continuous pain assessment

	Total n=6648	Tracheal ventilation n=2138	Non invasive ventilation n=1493	Spontaneous ventilation n=3017	P value*
Patient Characteristics					
Gestational age (weeks, mean ± SD)	35·0 ± 4·6	32·7 ± 5·2	33·8 ± 3·8	37·3 ± 3·1	< 0·001
24-29, number (%)	1045 (15·7)	775 (36·3)	214 (14·3)	56 (1·9)	< 0·001**
30-32, number (%)	1011 (15·2)	360 (16·8)	451 (30·2)	200 (6·6)	-
33-36, number (%)	1853 (27·9)	389 (18·2)	486 (32·6)	978 (32·4)	-
37-42, number (%)	2737 (41·2)	613 (28·7)	342 (22·9)	1782 (59·1)	-
Birth weight (grams)Mean ± SD	2385 ± 1008	1950 ± 1035	2133 ± 892	2817 ± 856	< 0·001
Male, number (%)	3753 (56·5)	1257 (58·8)	841 (56·3)	1655 (54·9)	0·087
Inborn, number (%)	5340 (80·3)	1457 (68·1)	1306 (87·5)	2577 (85·4)	< 0·001
Type of delivery- number (%)					
Vaginal	3051 (46·0)	877 (41·3)	569 (38·1)	1605 (53·3)	< 0·001

Caesarean	3577 (54·0)	1247 (58·7)	922 (61·8)	1408 (46·7)	-
Age at admission (hr, median (IQR)	1·0 (0·3-12·1)	0·8 (0·3-8·3)	0·5 (0·2-1·7)	3·0 (0·4-26·8)	< 0·001
CRIB score† (median (IQR))	0 (0-2)	2 (1-5)	0 (0-1)	0 (0-0)	< 0·001
5-min Apgar Score (mean ± SD)	8·4 ± 1·9	7·4 ± 2·4	8·5 ± 1·4	9·0 ± 1·3	< 0·001
Intubated at admission, number (%)	1372 (20·6)	1372 (64·2)	NA	NA	NA
Died during study, number (%)	210 (3·2)	200 (9·4)	3 (0·2)	7 (0·2)	< 0·001
NICU Length of stay (days)‖ (median (IQR))	8 (3-20)	14 (6-28)	11 (5-26)	5 (3-11)	< 0·001
Pain assessments, number (%)††	2113 (31·8)	984 (46·0)	523 (35·0)	606 (20·1)	< 0·001

NICU=neonatal intensive care unit. NA=not applicable. CRIB=Clinical Risk Index for Babies. †The CRIB score is a measure of

illness severity, based on clinical data from the first 12 hours after birth (range: 0 to 23, higher scores indicate great risk of mortality).

*Comparisons of the three types of ventilation were done with χ2 (Fisher's exact test when required), ANOVA, or Kruskal-Wallis test.

**χ2 for distributions in all strata of gestational ages within the three ventilation groups. ‖Data collection was stopped on day 28 of

hospital stay; 1036 (15·6%) of 6647 neonates were hospitalised for longer than 28 days. Discharge data were missing for one patient.

††Only assessments carried out with continuous, ongoing pain scales were included.

Table 2. Frequency of continuous pain assessments in participating countries and by ventilation group

Country	Centers performing pain assessment** number (%)	Number of pain assessments per neonate per day*** Mean (SD)	Neonates with at least one pain assessment during NICU stay, number (%)				P value*
			All neonates n= 6648	Tracheal ventilation n=2138	Non invasive ventilation n=1493	Spontaneous ventilation n=3017	
Austria	1/4 (25·0)	0·8 (0·7)	31/73 (42·5)	8/22 (36·4)	20/32 (62·5)	3/19 (15·8)	**0·004**
Belgium	3/4 (75·0)	1·3 (1·4)	29/128 (22·7)	16/37 (43·2)	9/51 (17·6)	4/40 (10·0)	**0·001**
Cyprus	0/1 (0·0)	0	0/84 (0·0)	0	0	0	-
Estonia	0/2 (0·0)	0	0/22 (0·0)	0	0	0	-
Finland	1/6 (16·7)	2·3 (0·8)	18/201 (9·0)	3/52 (5·8)	5/45 (11·1)	10/104 (9·6)	0·619
France	34/34 (100·0)	2·6 (1·8)	779/885 (88·0)	445/493 (90·3)	192/222 (86·5)	142/170 (83·5)	**0·047**
Germany	1/4 (25·0)	0·8 (0·8)	2/126 (1·6)	2/29 (6·9)	0/17 (0·0)	0/80 (0·0)	**0·033**
Greece	0/13 (0·0)	0	0/455 (0·0)	0	0	0	-
Italy	20/28 (71·4)	1·4 (1·4)	236/422 (55·9)	93/131 (71·0)	84/150 (56·0)	59/141 (41·8)	**<0·001**

Lithuania	0/1 (0·0)	0	0/45 (0·0)	0	0	0	-
Malta	0/1 (0·0)	0	0/28 (0·0)	0	0	0	-
Netherlands	4/5 (80·0)	1·6 (0·8)	166/208 (79·8)	56/69 (81·2)	55/68 (80·9)	55/71 (77·5)	0·832
Norway	3/16 (18·8)	1·1 (0·9)	29/334 (8·7)	3/35 (8·6)	7/94 (7·4)	19/205 (9·3)	0·874
Poland	2/8 (25·0)	2·7 (1·3)	30/83 (36·1)	11/50 (22·0)	14/25 (56·0)	5/8 (62·5)	**0·004**
Portugal	10/14 (71·4)	3·1 (2·6)	140/236 (59·3)	36/55 (65·5)	29/54 (53·7)	75/127 (59·1)	0·457
Spain	5/30 (16·7)	1·8 (1·3)	28/468 (6·0)	14/202 (6·9)	8/149 (5·4)	6/117 (5·1)	0·750
Sweden	2/6 (33·3)	6·7 (3·9)	27/160 (16·9)	21/38 (55·3)	4/47 (8·5)	2/75 (2·7)	**<0·001**
United Kingdom	30/66 (45·5)	5·7 (6·0)	598/2690 (22·2)	276/713 (38·7)	96/438 (21·9)	226/1539 (14·7)	**<0·001**
TOTAL	116/243 (47·7)	3·3 (3·9)	2113/6648 (31·8)	984/2138 (46·0%)	523/1493 (35·0)	606/3017 (20·1)	**<0·001**

*Comparisons of 3 types of ventilation using $\chi2$; **at least in one neonate; ***in neonates who had at least 1 assessment for continuous pain during their entire NICU stay.

Table 3. NICU characteristics associated with assessments of continuous pain

	All centers				
	Univariable analysis¶			*Multivariable analysis***	
	No pain assessment (n=110) n (%)§	Pain assessment (n=93) n (%)§	Chi² or Mann Whitney U test	Odds ratio (95% CI)	P value
Local neonatal pain assessment guidelines in 2012			**<0·001**		**<0·001**
No, (n=80)	61 (76·3)	19 (23·8)		1*	
Yes, (n=123)	49 (39·8)	74 (60·2)		3·96 (2·11-7·46)	
Local neonatal pain/sedation treatment guidelines in 2012			**0·001**	Not Included[a]	
No, (n=50)	37 (74·0)	13 (26·0)			

Yes, (n=153)	73 (47·7)	80 (52·3)			
Physician pain champion§§			**<0·001**	Not Included[b]	
No, (n=127)	83 (65·4)	44 (34·6)			
Yes, (n=76)	27 (35·5)	49 (64·5)			
Nurse pain champion§§			**<0·001**		**0·009**
No, (n=107)	72 (67·3)	35 (32·7)		1*	
Yes, (n=96)	38 (39·6)	58 (60·4)		2·54 (1·27-5·11)	
Hospital pain management team or consult service			**0·001**		0·510
No, (n=71)	50 (70·4)	21 (29·6)		1*	
Yes, (n=132)	60 (45·5)	72 (54·5)		1·36 (0·55-3·38)	
Parents allowed 24 hours a day			0·939	Not Included[c]	
No, (n=41)	22 (53·7)	19 (46·3)			
Yes, (n=162)	88 (54·3)	74 (45·7)			
Number of beds in the unit,	20 (14-29) †	18 (13-26) †	0·352	Not Included[c]	

(n=203)				
Number of medical admissions per year, (n=203)	453 (300-631)†	384 (277-600) †	0·192	Not Included[c]	
Number of surgical admissions per year, (n=203)	0 (0-30) †	20 (0-69) †	**<0·001**	1·01 (1·00-1·02)	**0·007**
Number of ventilator-days per year, (n=203)	312 (115-701) †	672 (216-1515) †	**<0·001**	1·00 (1·00-1·00)	0·178

NICU=neonatal intensive care unit. §Unless indicated otherwise. †Median (IQR). §§Locally designated. ¶Univariate analysis data are for the 203 centers that were included in the multivariable analysis. Other centers were eliminated because of missing data.

*Reference category, ** Generalized Estimation Equation model with country as the cluster.

a: Non included in the model because this variable was highly correlated with local neonatal pain assessment guidelines.

b: Non included in the model because this variable was highly correlated with the presence of a nurse pain champion.

c: Non included in the model because this variable was not significant in univariate analysis.

Table 4. Patient characteristics associated with assessments of continuous pain in all neonates

	Univariable analysis¶			Multivariable analysis**	
	Pain assessment not performed n=4354	Pain assessment performed § n=1949	p value***	Odds ratio (95% CI)	P value
Sex			0·449	Not Included[a]	
Male, number (%), n=3559	2445 (68·7)	1114 (31·3)			
Female, number (%), n=2739	1906 (69·6)	833 (30·4)			
Gestational age (weeks)			**<0·001**		
37-42, number (%), n=2599	1951 (75·1)	648 (24·9)		1*	
33-36, number (%), n=1771	1305 (73·7)	466 (26·3)		1·10 (0·94-1·30)	0·232
30-32, number (%), n=967	559 (57·8)	408 (42·2)		2·11 (1·60-2·80)	**<0·001**
24-29, number (%), n=966	539 (55·8)	427 (44·2)		1·92 (1·39-2·64)	**<0·001**
Birthweight (grams) ,				Not Included[b]	

n=6302; Mean (SD)	2505 (991)	2151 (996)	**<0·001**		
IUGR			0·083	Not Included[a]	
No, number (%), n=5204	3619 (69·5)	1585 (30·5)			
Yes, number (%), n=1093	731 (66·9)	362 (33·1)			
Inborn			**<0·001**		**0·023**
No, number (%), n=1137	674 (59·3)	463 (40·7)		1*	
Yes, number (%), n=5166	3680 (71·2)	1486 (28·8)		0·67 (0·48-0·95)	
Age at admission (hours)			**<0·001**		
> 168, number (%), n=459	289 (63·0)	170 (37·0)		1*	
73-168, number (%), n=244	192 (78·7)	52 (21·3)		0·73 (0·48-1·11)	0·143
25-72, number (%), n=472	345 (73·1)	127 (26·9)		1·09 (0·83-1·43)	0·533
7-24, number (%), n=709	518 (73·1)	191 (26·9)		0·96 (0·66-1·39)	0·820
<7, number (%), n=4419	3010 (68·1)	1409 (31·9)		1·22 (0·91-1·63)	0·182
CRIB score†, n=6303 Median (IQR)	0 (0-1)	1 (0-2)	**<0·001**	0·95 (0·92-0·99)	**0·013**

Apgar Score at 1 min, n=6284; Median (IQR)	8 (6-9)	7 (5-9)	**<0·001**	Not Included[c]	
APGAR at 5 min, n=6303 Median (IQR)	9 (8-10)	9 (7-10)	**0·002**	1·03 (0·99-1·08)	0·103
Already or immediately intubated at admission			**<0·001**		**<0·001**
No, number (%), n=5038	3711 (73·7)	1327 (26·3)		1*	
Yes, number (%), n=1265	643 (50·8)	622 (49·2)		1·97 (1·52-2·56)	
Surgery			**<0·001**		**0·028**
No, number (%), n=6192	4306 (69·5)	1886 (30·5)		1*	
Yes, number (%), n=111	48 (43·2)	63 (56·8)		2·14 (1·09-4·22)	
Respiratory distress syndrome			**<0·001**		**0·031**
No, number (%), n=4424	3147 (71·1)	1277 (28·9)		1*	
Yes, number (%), n=1879	1207 (64·2)	672 (35·8)		0·77 (0·61-0·98)	

Respiratory support‡			**<0·001**		
Spontaneous ventilation, number (%), n=2862	2302 (80·4)	560 (19·6)		1*	
Non-invasive ventilation, number (%), n=1448	949 (65·5)	499 (34·5)		1·88 (1·41-2·51)	**<0·001**
Tracheal ventilation, number (%), n=1993	1103 (55·3)	890 (44·7)		1·29 (0·97-1·70)	**0·079**
O-SH-GA drugs (continous and/or bolus)			**<0·001**		**<0·001**
No, number (%), n=4503	3381 (75·1)	1122 (24·9)		1*	
Yes, number (%), n=1800	973 (54·1)	827 (45·9)		1·99 (1·55-2·54)	
Length of NICU stay (days) ǁ, n=6303; Median (IQR)	8 (3-18)	9 (4-24)	**<0·001**	0·99 (0·97-1·00)	0·074

NICU=neonatal intensive care unit. O-SH-GA=opioids, sedatives/hypnotics, or general anesthetics. IUGR=intrauterine growth retardation. CRIB=Clinical Risk Index for Babies. CI=Confidence interval. SD=Standard Deviation. IQR=interquartile range.

§At least one continuous pain assessment during the entire NICU stay, ¶Univariable analysis data for the 6303 neonates that were included in the multivariable analysis

*Reference category; **Generalized Estimating Equations model with NICU as cluster; *** Comparisons were done with χ2 (Fisher's exact test when required), t-test or Mann-Whitney tests as appropriate.

†Odds ratio per point increase in CRIB score. The CRIB score is a measure of illness severity in neonates. It consists of 6 items collected in the first 12 hours after birth (range: 0 to 23, higher scores indicate great clinical risk of mortality).

‡Patients were classified in 3 groups according to the highest level of ventilation they received during the study period.

|| Data gathering was stopped on day 28 of hospital stay; 989 (15·7%) of 6303 neonates were hospitalised for longer than 28 days.

a: Non included in the model because this variable was not significant in univariate analysis.

b: Non included in the model because this variable was highly correlated with gestational age.

c: Non included in the model because this variable was highly correlated with Apgar scores at 5 minute.

Table 5. Patient characteristics associated with assessments of continuous pain assessments in tracheally ventilated newborns

	Univariable analysis¶			*Multivariable analysis***	
	Pain assessment not performed n=1104	Pain assessment performed § n=890	p value** *	Odds ratio (95% CI)	P value
Sex			0·428	Not Included[a]	
Male, number (%), n=1174	642 (54·7)	532 (45·3)			
Female, number (%), n=818	462 (56·5)	356 (43·5)			
Gestational age (weeks)			0·077	Not Included[a]	
37-42, number (%), n=571	322 (56·4)	249 (43·6)			
33-36, number (%), n=372	224 (60·2)	148 (39·8)			
30-32, number (%), n=338	186 (55·0)	152 (45·0)			
24-29, number (%), n=712	371 (52·1)	341 (47·9)			

Birthweight (grams) , n=1994 Mean (SD)	2002 (1042)	1920 (1022)	0·079	Not Included[a]	
IUGR			0·962	Not Included[a]	
No, number (%), n=1669	925 (55·4)	744 (44·6)			
Yes, number (%), n=322	178 (55·3)	144 (44·7)			
Inborn			**<0·001**		0·297
No, number (%), n=588	284 (48·3)	304 (51·7)		1*	
Yes, number (%), n=1406	820 (58·3)	586 (41·7)		0·83 (0·59-1·18)	
Age at admission (hours)			0·064	Not Included[a]	
> 168, number (%), n=172	84 (48·8)	88 (51·2)			
73-168, number (%), n=45	27 (60·0)	18 (40·0)			
25-72, number (%), n=88	42 (47·7)	46 (52·3)			
7-24, number (%), n=214	109 (50·9)	105 (49·1)			
<7, number (%), n=1475	842 (57·1)	633 (42·9)			
CRIB score†, n=1994				0·93 (0·90-0·97)	**0·001**

Mean (SD)	3·4 (3·7)	3·0 (3·1)	**0·015**		
APGAR at 1 min, n=1989 Median (IQR)	6 (4-8)	6 (3-8)	0·431	Not Included[a]	
APGAR at 5 min, n=1994 Median (IQR)	8 (6-9)	8 (6-9)	**0·020**	1·04 (0·99-1·09)	0·119
Already or immediately intubated at admission			**0·001**		**<0·001**
No, number (%), n=729	461 (63·2)	268 (36·8)		1*	
Yes, number (%), n=1265	643 (50·8)	622 (49·2)		2·00 (1·55-2·58)	
Surgery			**0·010**		0·256
No, number (%), n=1910	1069 (56·0)	841 (44·0)		1*	
Yes, number (%), n=84	35 (41·7)	49 (58·3)		1·53 (0·73-3·18)	
Respiratory distress syndrome			**0·016**		0·155
No, number (%), n=1020	538 (52·7)	482 (47·3)		1*	

Yes, number (%), n=974	566 (58·1)	408 (41·9)		0·83 (0·64-1·07)	
O-SH-GA drugs (continous and/or bolus)			**0·019**		**0·008**
No, number (%), n=438	264 (60·3)	174 (39·7)		1*	
Yes, number (%), n=1556	840 (54·0)	716 (46·0)		1·45 (1·10-1·92)	
Length of stay in NICU (days) ‖, n=1994 Median (IQR)	15 (6-28)	14 (6-28)	0·590	Not Included[a]	
Total duration of mechanical ventilation (hours) , n=1994 Median (IQR)	37 (11-112)	61 (20-142)	**<0·001**	1·00 (1·00-1·00)	**0·001**
Number of ventilator-free days‡, n=1994 Median (IQR)	23 (8-26)	23 (14-26)	0·777	Not Included[a]	

NICU=neonatal intensive care unit. O-SH-GA=opioids, sedatives/hypnotics, or general anesthetics. IUGR=intrauterine growth retardation. CRIB=Clinical Risk Index for Babies. CI=Confidence interval. SD=Standard Deviation. IQR=interquartile range.

§At least one assessment of continuous pain during the NICU stay, ¶Univariable analysis data for the 1994 neonates that were included in the multivariable analysis.

*Reference category; **Generalized Estimation Equation model with NICU as cluster; *** Comparisons were done with χ2 (Fisher's exact test when required), t-test or Mann-Whitney tests as appropriate.

†Odds ratio per point increase in CRIB score. The CRIB score is a measure of illness severity in neonates. It consists of 6 items collected in the first 12 hours after birth (range: 0 to 23, higher scores indicate great clinical risk of mortality).

||Data collection was stopped on day 28 of hospital stay: 566 (28·4%) of 1994 neonates were hospitalised for longer than 28 days.

a: Non included in the model because this variable was not significant in the univariable analysis.

‡Ventilator-free days were defined as the number of calendar days from the time of tracheal extubation to day 28 after NICU admission. If a neonate was reintubated and subsequently extubated before day 28, ventilator-free days were counted from the end of the last period of tracheal intubation. If a neonate was still receiving tracheal ventilation on day 28 or had died before day 28, then 0 ventilator-free days were noted. For neonates discharged before day 28 of admission, ventilator-free days were zero if the neonate was still intubated at discharge (transfer) and ventilator-free days were counted from the time of tracheal extubation to day 28 after NICU admission if the neonate was already extubated at discharge.

Figure Legends

Figure 1:

Flow chart of the countries invited, the participating NICUs ("units"), patients assessed, and those enrolled in this study. All neonates with pain assessment outcome data were included in our analyses; missing data were not imputed.

Figure 2:

Frequency of assessments of continuous pain in the tracheal ventilation group on patient-days with or without tracheal ventilation, or with or without the use of O-SH-GA drugs. Data from all ventilated neonates (n=2138) were analyzed for the 33,625 patient-days of observation. *P* values are based on χ^2-tests.
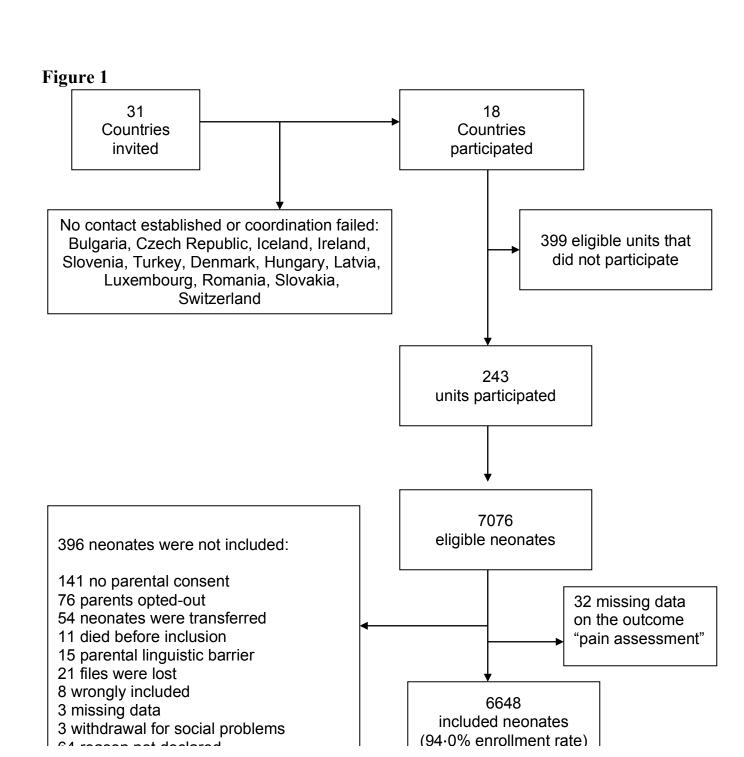
Figure 1

Figure 2