
Article:
Gravesteijn, BY, Sewalt, CA, Ercole, A et al. (166 more authors) (2019) Variation in the practice of tracheal intubation in Europe after traumatic brain injury : a prospective cohort study. Anaesthesia, 75 (1). pp. 45-53. ISSN 0003-2409

https://doi.org/10.1111/anae.14838

Original Article

Variation in the practice of tracheal intubation in Europe after traumatic brain injury: a prospective cohort study

B. Y. Gravesteijn,[1] **C. A. Sewalt,**[2] **A. Ercole,**[3] **F. Lecky,**[4] **D. Menon,**[5] **E. W. Steyerberg,**[6] **A. I. R. Maas,**[7] **H. F. Lingsma,**[8] **M. Klimek**[9] and **the CENTER-TBI collaborators***

1 PhD Student, Departments of Anesthesiology and Public Health 2 PhD Student, 8 Associate professor, Department of Public Health, 9 Vice-Chairman/Vice-Head Residency Training, Department of Anesthesiology, Erasmus University Medical Centre, Rotterdam, The Netherlands
3 Consultant in Anaesthesia and Intensive Care, Department of Anaesthesiology, University of Cambridge, UK
4 Professor, Emergency Medicine Research in Sheffield, School of Health and Related Research, Faculty of Medicine, Dentistry and Health, University of Sheffield, Sheffield, UK
5 Professor, Department of Anaesthesia, University of Cambridge, UK
6 Professor, Department of Biostatistics, Leiden University Medical Centre, Leiden, the Netherlands
7 Professor, Department of Neurosurgery, University Hospital Antwerp, Antwerp, Belgium

Summary

Traumatic brain injury patients frequently undergo tracheal intubation. We aimed to assess current intubation practice in Europe and identify variation in practice. We analysed data from patients with traumatic brain injury included in the prospective cohort study collaborative European neurotrauma effectiveness research in traumatic brain injury (CENTER-TBI) in 45 centres in 16 European countries. We included patients who were transported to hospital by emergency medical services. We used mixed-effects multinomial regression to quantify the effects on pre-hospital or in-hospital tracheal intubation of the following: patient characteristics; injury characteristics; centre; and trauma system characteristics. A total of 3843 patients were included. Of these, 1322 (34%) had their tracheas intubated; 839 (22%) pre-hospital and 483 (13%) in-hospital. The fit of the model with only patient characteristics predicting intubation was good (Nagelkerke R2 64%). The probability of tracheal intubation increased with the following: younger age; lower pre-hospital or emergency department GCS; higher abbreviated injury scale scores (head and neck, thorax and chest, face or abdomen abbreviated injury score); and one or more unreactive pupils. The adjusted median odds ratio for intubation between two randomly chosen centres was 3.1 (95%CI 2.1–4.3) for pre-hospital intubation, and 2.7 (95%CI 1.9–3.5) for in-hospital intubation. Furthermore, the presence of an anaesthetist was independently associated with more pre-hospital intubation (OR 2.9, 95%CI 1.3–6.6), in contrast to the presence of ambulance personnel who are allowed to intubate (OR 0.5, 95%CI 0.3–0.8). In conclusion, patient and injury characteristics are key drivers of tracheal intubation. Between-centre differences were also substantial. Further studies are needed to improve the evidence base supporting recommendations for tracheal intubation.

Correspondence to: B. Y. Gravesteijn
Email: b.gravesteijn@erasmusmc.nl
Accepted: 12 August 2019
Keywords: Europe; guideline; practice variation; tracheal intubation; traumatic brain injury
This article is accompanied by an editorial by Lockey and Wilson, *Anaesthesia* 2019; https://doi.org/10.1111/anae.14854.
*See Appendix S1 for the full list of collaborators.
Twitter: @BGravesteijn; @charliesewalt; @AriErcole; @Menon_Cambridge; @Esteyerberg; @hesterlingsma

Introduction

The burden of traumatic brain injury (TBI) is high; it is a leading cause of injury-related death and disability [1]. Although the rates vary between countries, TBI is estimated to be responsible for around 300 hospital admissions and 12 deaths per 100,000 persons per year in Europe [2]. Although the primary brain injury is defined by the trauma itself, secondary brain injury – especially due to hypoxia and hypotension – must be prevented [3–5]. Secondary insults might be prevented by securing the airway, by intubating the tracheas of patients with a depressed level of consciousness, compromised airway reflexes and induced central respiratory depression [6–9] to protect the airway and sustain normoxia and normocapnia [10, 11].

There are also potential risks of intubation. Injudicious use of anaesthetic agents required for intubation and positive pressure ventilation can cause hypotension, particularly in hypovolaemic trauma patients [12]. On the other hand, inadequate depth of anaesthesia during laryngoscopy may precipitate hypertension and lead to surges in blood pressure and/or intra-cranial pressure (ICP) [13]. Moreover, failure to rapidly control the airway may lead to hypoxia or hypercapnia. These insults (hypotension, intra-cranial hypertension and hypoxia) may all cause harm [4, 14–17].

There are few data available regarding which patients should have their airways secured. Although a GCS $\leq$ 8 is generally considered as the threshold for mandatory tracheal intubation [11, 18, 19], there is little evidence to support this recommendation. Traumatic brain injury intubation guidelines are based primarily on level-3 evidence [11]. The only exception is a randomised controlled trial recommending pre-hospital intubation in TBI patients with a GCS $\leq$ 9 [20]. Rates of adherence to guidelines for pre-hospital intubation are around 80%, with a wide range of 44–92% reported in the literature [21, 22]. This lack of evidence and low adherence to guidelines could possibly result in differences in local intubation protocols or preferences.

We aimed to gain insights into the current practice of tracheal intubation after TBI across Europe by conducting this prospective cohort study, and to quantify the effects of: patient and trauma factors; centre; and trauma system characteristics on intubation practice.

Methods

This study conforms with the STROBE reporting guidelines [23]. Data from the collaborative European neurotrauma effectiveness research in TBI (CENTER-TBI) were used [24]. In brief, CENTER-TBI was a prospective cohort study comprising 4509 patients with TBI of all severities. Traumatic brain injury patients presenting within 24 h after injury to one of the 61 participating study sites in Europe (mainly level-1 trauma centres), or referred from another hospital to the participating study site within 24 h, were eligible for this study. We collected data from December 2014 until 2018. More details, including details concerning ethics approval, have previously been reported [24].

For this analysis, we did not include patients who self-presented to the study site, because pre-hospital intubation can only be considered by medical services. We also did not include patients presenting to hospitals that included fewer than 20 patients, to allow for reliable statistical analysis. Although an intensive phase of data cleaning had already been completed, the CENTER-TBI database continues to be improved whenever data entry errors are found. Data for the CENTER-TBI study were collected through the Quesgen e-CRF (Quesgen Systems Inc, Burlingame, CA, USA), hosted on the INCF platform and extracted via the INCF Neurobot tool (INCF, Stockholm, Sweden). We used Version 1.1 of the database for this analysis.

We defined in-hospital intubation by the variables that described whether a patient had their trachea intubated in the referring hospital (if they were referred), or in the study hospital. Pre-hospital intubation was defined by the variable that described whether a patient received pre-hospital intubation. All other patients were considered as having not had their tracheas intubated.

Since we were interested in the effect of baseline characteristics on both in-hospital and pre-hospital intubation, we mostly considered predictors that could influence both. However, readily available vital signs such as oxygen saturation or respiratory rate in the pre-hospital setting were not taken into account because they were not registered in the study. Instead, the baseline patient and trauma characteristics which were considered for the models included: age; the thorax, abdominal, facial and head and neck anatomical subscales abbreviated injury scale (AIS) of the injury severity score (ISS); the highest pre-hospital or emergency department (ED) GCS; and pre-hospital pupil reactivity.

Every participating study centre completed provider profiling questionnaires to gain insight into general operational structures and treatment policies for trauma patients. Details and the design of the questionnaires have previously been described [25–27]. For this study, we used questions that addressed the trauma system or policies regarding intubation. These included whether the physician on the pre-hospital care team

was an anaesthetist, whether the ambulance personnel were trained to intubate without drugs and whether the policy on scene was best described as 'stay-and-play' (giving treatment for stabilisation before transportation) or 'scoop-and-run' (transport the patient as quickly as possible to the hospital).

The data analysis plan was approved by the management committee of the CENTER-TBI study before commencement. Firstly, we compared patient and trauma characteristics of patients whose tracheas were intubated in the pre-hospital setting, in the in-hospital setting and patients whose tracheas were not intubated. Categorical variables were compared using Chi-square tests, or Fisher's exact test where appropriate. We tested continuous variables with one-way ANOVA or Kruskall–Wallis tests. The correlation between incidence of pre-hospital intubation and in-hospital intubation per centre was calculated with the Spearman's correlation coefficient.

For the models predicting intubation, we imputed missing data with a multiple imputation method (five datasets), using the MICE package [28], assuming data to be missing at random. The imputation model included relevant predictors and the outcome (intubation). After imputation, patients with missing outcome (intubation) were not included ('imputation then deletion') [29].

We used multinomial regression models to study associations with pre-hospital and in-hospital intubation. Candidate variables were selected based on the descriptive analysis ($p < 0.05$) and clinical knowledge, and were then included in the model. We did not categorise continuous variables.

Subsequently, the models, including patient and trauma characteristics, were extended with random intercepts for centre, conditional on country, to estimate the difference in probability of intubation between centres. Finally, we added the relevant trauma system characteristics from the provider profiling questionnaires to the model.

The different models were compared using the Nagelkerke R2 as a measure for explained variance. The mean log-likelihood of the fitted models was compared with the log-likelihood of the null model [30]. To quantify the between-centre and between-country differences in intubation, we calculated the median odds ratio [31]. The median odds ratio can be interpreted as the odds ratio for intubation in two randomly selected centres or countries, comparing the high risk with the low-risk group. The estimates and standard errors of the random intercepts and variance of the random intercepts were pooled using Rubin's rules [32].

Two sensitivity analyses were performed. First, we performed a complete case sensitivity analysis, not including patients with some missing value in any of the predictors or outcome. The results were compared with the analysis on the imputed dataset, to observe whether imputation changed the effect estimates. Second, a sensitivity analysis was performed by not including the patients who underwent in-hospital tracheal intubation in a referring hospital. This was done to observe whether the two in-hospital intubated groups were comparable.

We performed the analyses using R (R Foundation for Statistical Computing, Vienna, Austria). For the multinomial model, the 'multinom' function from the 'nnet' package was used. The mixed-effects multinomial regression was performed using the PROC GLIMMIX function in SAS (SAS Institute Inc. SAS, Cary, NC, USA) [33]. The code can be found on https://github.com/ErasmusCMB/CENTER-TBI/blob/master/final_script_pv_intub.Rmd.

Results

After excluding patients who did not arrive by medical services (n = 487), patients from centres with fewer than 20 patients (n = 176) and patients from whom no information on intubation was present (n = 3), we included 3843 patients from 45 centres in the analysis (Fig. 1). The median number of patients was 62 per centre, and 115 per country (Fig. 2).

In total, 839 (22%) had their tracheas intubated in the pre-hospital setting, while 483 (13%) had their tracheas intubated in hospital, of which 194 (40%) were performed in the referring hospital. The observed pre-hospital intubation rates differed from 0% to 60% between centres, and from 2% to 56% between countries. In-hospital intubation rates differed from 0% to 73% between centres, and from 1% to 41% between countries (Fig. 3). Centres who performed more pre-hospital intubation did not perform more or less in-hospital intubation (rho = 0.05, p = 0.73).

Patients whose tracheas were intubated had lower pre-hospital motor GCS, median (IQR [range]) 3 (1–5 [1–6]) and higher ISS than patients whose tracheas were not intubated. The pre-hospital intubation group most often had one or two non-reactive pupils (187, 29%), followed by the in-hospital intubation group. Patients in the pre-hospital intubation group were 7.0 (95%CI 5.1–8.2) years younger than the other groups. Road traffic incident was the cause of injury in the majority of the pre-hospital intubation group (458, 56%), whereas falls were more common in the other groups; 195 (43%) in the in-hospital intubation group and 1195 (48%) in the group who were not intubated. The pre-hospital time was 0.3 h longer in

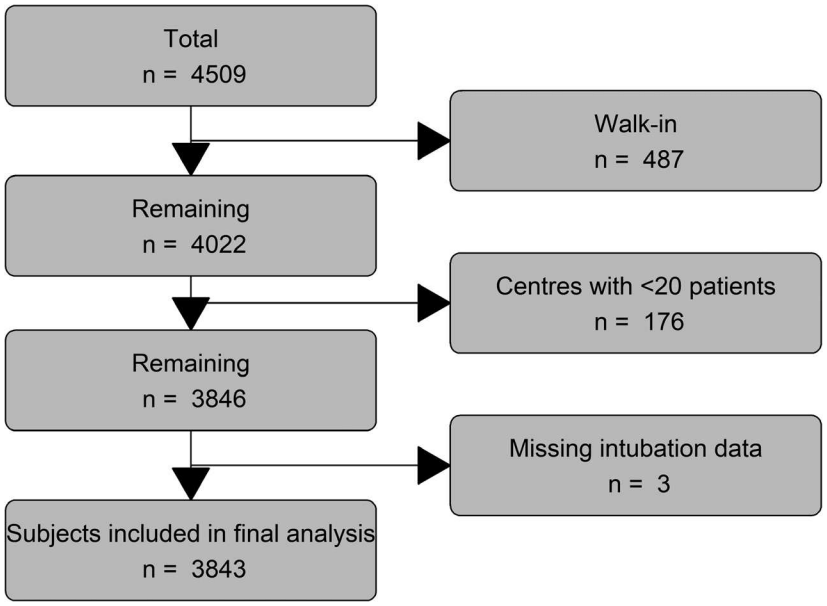


Figure 1 Flow chart of patients included in this analysis.

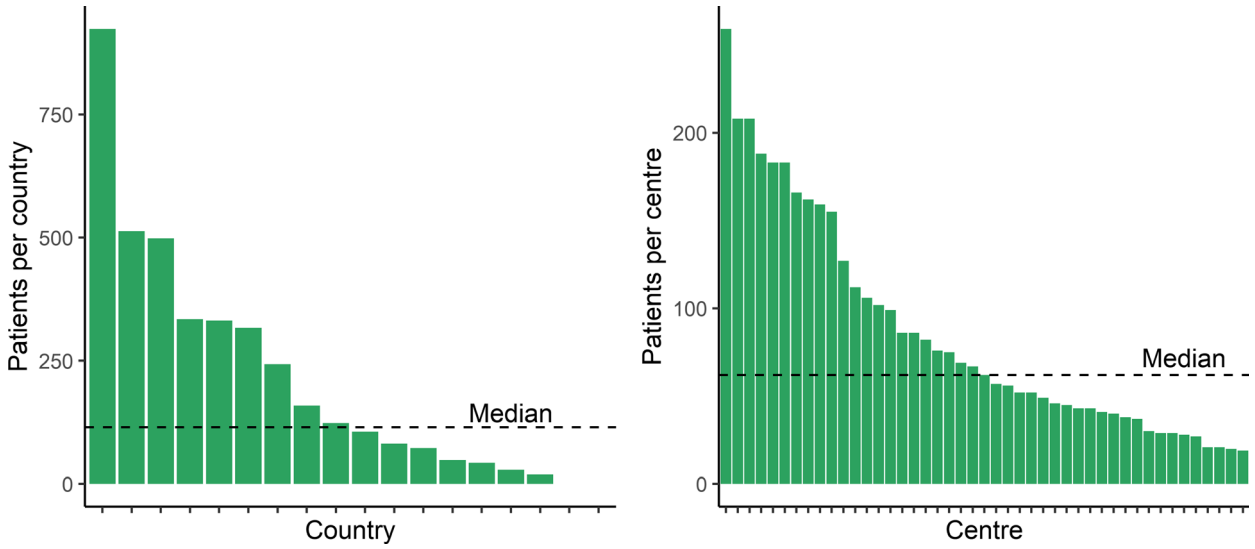


Figure 2 Number of observations per participating country and centre. The median is displayed (62 per centre, 115 per country).

the pre-hospital intubation group (95%CI 0.2–0.3 h). The travel time, however, was similar in all groups; the median was 0.3 (0.2–0.5 [0–1.37]), 0.2 (0.2–0.4 [0–1.37]) and 0.3 (0.2–0.4 [0–1.37]) h in the pre-hospital, in-hospital and no intubation groups, respectively. The highest proportion of missing values was seen for the pupil assessments (43% pre-hospital, 50% in-hospital) and the travel time (50%) (Table 1).

Consecutively, we fitted the model with seven predictors of intubation (Fig. 5). The strongest predictor was GCS (OR 0.57, 95%CI 0.55–0.59 per point increase in GCS for pre-hospital intubation, and OR 0.64, 95%CI 0.62–0.67 for in-hospital intubation). The model with GCS only already had a good fit on the data; the Nagelkerke R2 was 60%. Pre-hospital unreactive pupil(s) increased the odds of pre-hospital intubation (OR 3.0, 95%CI 1.5–6.0), but not for

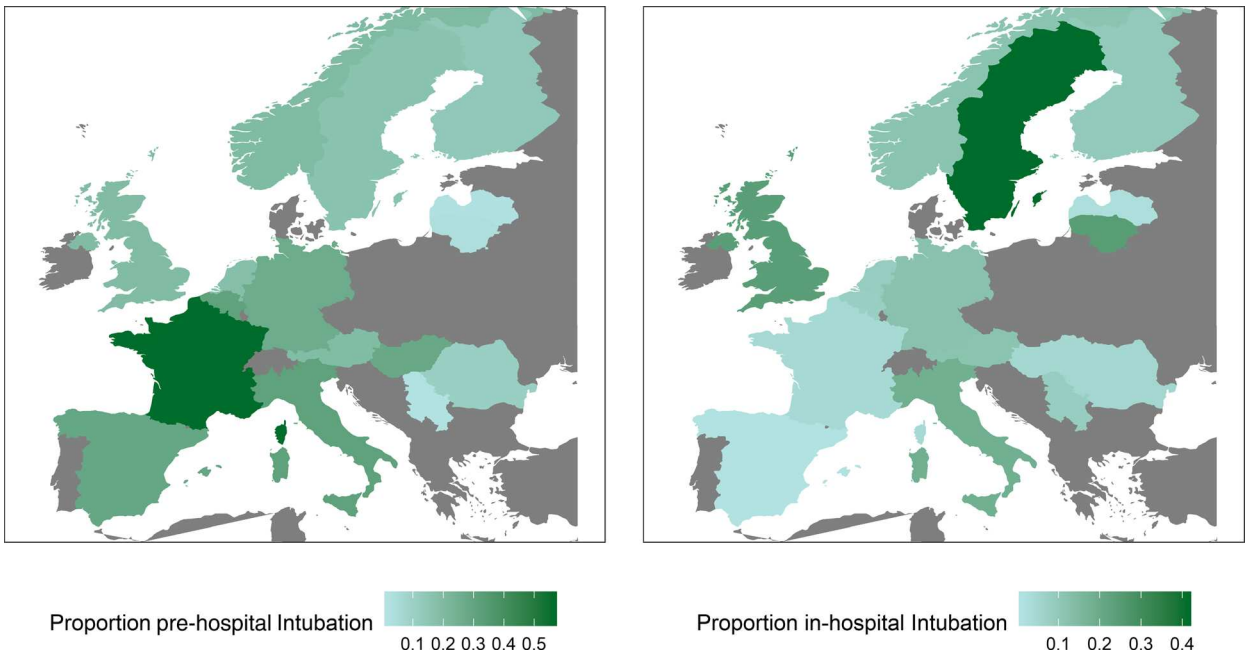


Figure 3 Proportion of pre-hospital and in-hospital patients who had their tracheas intubated across Europe.

in-hospital intubation (OR 1.0, 95%CI 0.5–2.0). Higher AIS increased the odds for intubation; the strongest predictors of the AIS were thorax and chest AIS (OR 1.5, 95%CI 1.4–1.6 per point increase for pre-hospital intubation, and OR 1.3, 95%CI 1.1–1.4 for in-hospital intubation) and face AIS (OR 1.3, 95%CI 1.2–1.5 per point increase for pre-hospital intubation, and OR 1.3, 95%CI 1.2–1.4 for in-hospital intubation). Finally, age lowered the odds of pre-hospital intubation (OR 0.98, 95%CI 0.98–0.99 per decade), but not of in-hospital intubation (OR 0.99, 95%CI 0.99–1.00). These predictors, other than GCS, increased the fit of the model to 64% (Table S1). A complete case analysis of this model showed the same magnitude and direction of the associations (Table S2). Similarly, a sensitivity analysis not including patients whose tracheas were intubated in a referring hospital showed the same magnitude and directions of the associations (Table S3).

The fit of the model increased to 71% with the inclusion of country and centre, indicating substantial practice variation. The median odds ratio between two randomly chosen centres was 3.1 (95%CI 2.1–4.3) for pre-hospital intubation and 2.7 (95%CI 1.9–3.5) for in-hospital intubation (Table S1). The predicted probability for an average patient to undergo pre-hospital intubation was highest in the south and west of Europe, and the probability of undergoing in-hospital intubation was higher in northern Europe (Fig. 4).

The variation attributable to centre was partly explained by trauma system characteristics. In particular, trauma system characteristics were strongly associated with pre-hospital intubation; the odds of pre-hospital intubation were larger (OR 2.9, 95%CI 1.3–6.6) when the physician on the pre-hospital care team was an anaesthetist, smaller (OR 0.5, 95%CI 0.3–0.8) when the ambulance personnel were allowed to intubate without drugs and smaller still (OR 0.1, 95%CI 0.0–0.4) when the main policy was scoop-and-run, instead of stay-and-play (Fig. 5 and Table S1).

Discussion

This study provides insights into current intubation practice for TBI patients in Europe. We found that the main driver of intubation was the GCS. However, other patient and trauma characteristics were also important regarding the decision to intubate, such as unreactive pupils, face injury and thorax and chest injury. In addition, this study describes significant variations in tracheal intubation practice between centres and countries in Europe; the effect of centre on the odds of intubation was similar to the effect of unreactive pupils. This large variation could be partially explained by trauma system characteristics.

The finding that other patient characteristics besides GCS played a role in the decision to intubate contrasts with current guidelines. Currently, international guidelines include only GCS as an objective clinical parameter with a specific threshold for intubation [11]. Therefore, it is a self-fulfilling prophecy that this patient characteristic should explain the majority of the variation. However, the

Table 1 Baseline characteristics. Values are number (proportion) or median (IQR [range]).

	Pre-hospital intubation n = 839	In-hospital intubation n = 483	Not intubated n = 2521	Missing data
Trachea intubated in referring hospital	–	194 (40.2%)	–	–
Age; years	44 (25–60 [3–92])	52 (31–68 [0–95])	53 (33–68 [1–94])	0%
Male	616 (73.4%)	353 (73.1%)	1639 (65.0%)	0%
BMI; $cm.kg^{-2}$	24.7 (22.6–27.7 [14–52])	24.7 (22.6–27.6 [15–42])	24.8 (22.3–27.6 [13–57])	32%
Total injury severity score	35 (25–50 [1–75])	29 (25–41 [1–75])	13 (8–18 [1–75])	1%
Head/neck AIS	3 (0–4 [0–6])	2 (0–5 [0–6])	1 (0–3 [0–6])	0%
Thorax/chest AIS	2 (0–3.5 [0–5])	0 (0–3 [0–5])	0 (0–0 [0–5])	0%
Face AIS	0 (0–3 [0–6])	0 (0–2 [0–5])	0 (0–1 [0–5])	0%
Abdomen/pelvis AIS	0 (0–0 [0–5])	0 (0–0 [0–6])	0 (0–0 [0–5])	0%
Cause of injury				
RTI	458 (55.9%)	178 (39.1%)	919 (37.1%)	2%
Fall	265 (32.4%)	195 (42.9%)	1195 (48.2%)	
Other	54 (6.6%)	45 (9.9%)	203 (8.2%)	
Violence	42 (5.1%)	37 (8.1%)	161 (6.5%)	
Highest pre-hospital mGCS	3 (1–5 [1–6])	5 (3–6 [1–6])	6 (6–6 [1–6])	34%
mGCS at arrival at the first ED	1 (1–1 [1–6])	5 (1–6 [1–6])	6 (6–6 [1–6])	22%
Most predictive GCS	4 (3–8 [3–15])	8 (5–13 [3–15])	15 (14–15 [3–15])	4%
GCS >12	74 (9.7%)	117 (25.2%)	2236 (90.2%)	4%
Pupil(s) unreactive pre-hospital	187 (28.9%)	28 (11%)	28 (2.1%)	43%
Pupils unreactive in-hospital	227 (40.4%)	52 (23.2%)	37 (3.3%)	50%
Pre-hospital time; h	1.3 (1.0–1.7 [0–5])	1.0 (0.7–1.3 [0–4])	1.0 (0.7–1.4 [0–5])	8%
Travel time; min	0.3 (0.2–0.5 [0–1])	0.2 (0.2–0.4 [0–1])	0.3 (0.2–0.4 [0–1])	50%

Every variable differed significantly between the groups ($p < 0.001$).
BMI, body mass index; AIS, abbreviated injury scale; RTI, road traffic incident; mGCS, motor component of the Glasgow Coma Score; ED, emergency department.

substantial added effects of additional clinical parameters in our models indicates that, in practice, the decision is also based on other factors. An illustrative example is the absence of pupillary reflexes, which indicate compromised brainstem function and therefore potentially jeopardised airway reflexes. Another example is the severity of facial injury, which could be suggestive of airway obstruction. Further research should focus on whether they could be included as indications for intubation.

Another finding of this study is the large regional variations in frequency of tracheal intubation. We found that these differences might be caused by regional differences in the composition of pre-hospital care teams, and their experience of intubation.

In particular, this study found that the availability of pre-hospital personnel who are skilled in pre-hospital intubation without drugs, actually lowered the chances of intubation. In the CENTER-TBI study, 43% of the centres indicated that personnel on the ambulance were able to intubate on scene without drugs [27]. These trauma systems might consist of more intensively trained ambulance personnel, often operating without the assistance of a physician. However, since they are not allowed to perform tracheal intubation with drugs, they can only do so on moribund patients (GCS of 3). Since the majority of moderate to severe TBI patients still have (partially) intact motor GCS responses in the pre-hospital setting [34], they would not be eligible for intubation in these trauma systems, explaining the lower overall intubation rates.

On the other end of the spectrum, we found that involvement of anaesthetists, with extensive training in intubation, increased the probability of intubation. Experience decreases the risk of harmful intubation, especially in non-elective settings [35, 36]. However, it is undesirable that the indication for intubation is the presence of specific professionals, instead of patient and trauma characteristics.

Our study confirms that, in the TBI field, paucity of evidence often results in low adherence to guidelines [21].

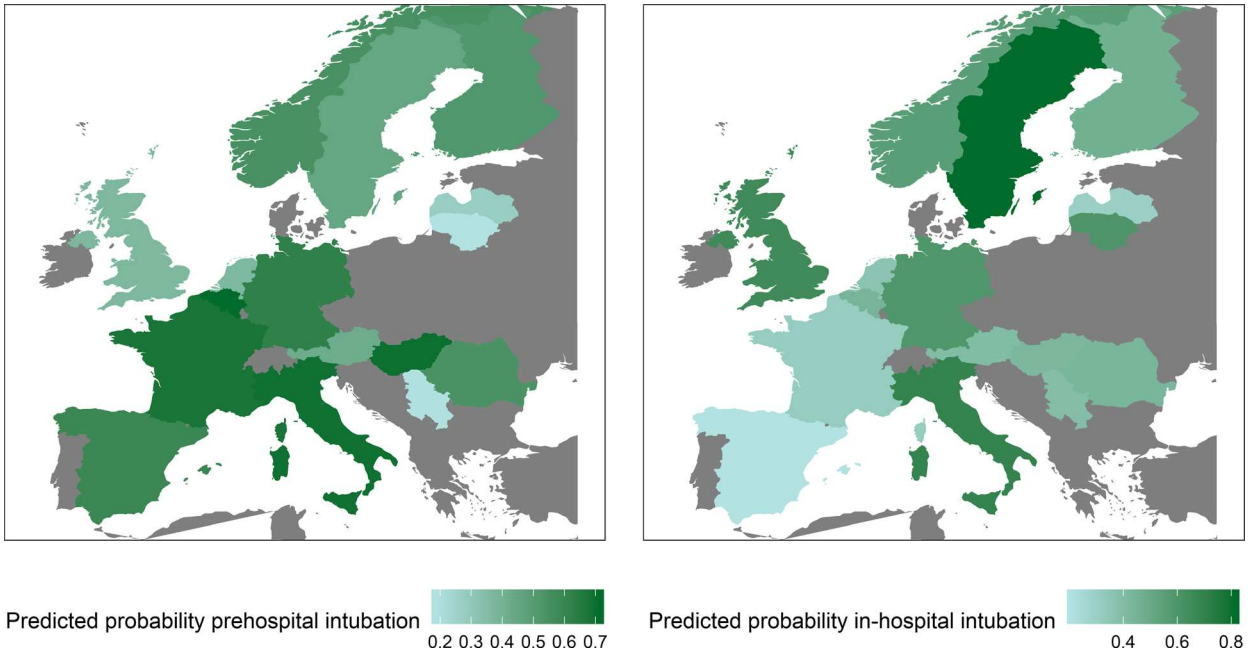


Figure 4 Intubation practice variation. The left panel shows the predicted probabilities of pre-hospital tracheal intubation for the average patient in each country, and the right panel shows the same result for in-hospital intubation.

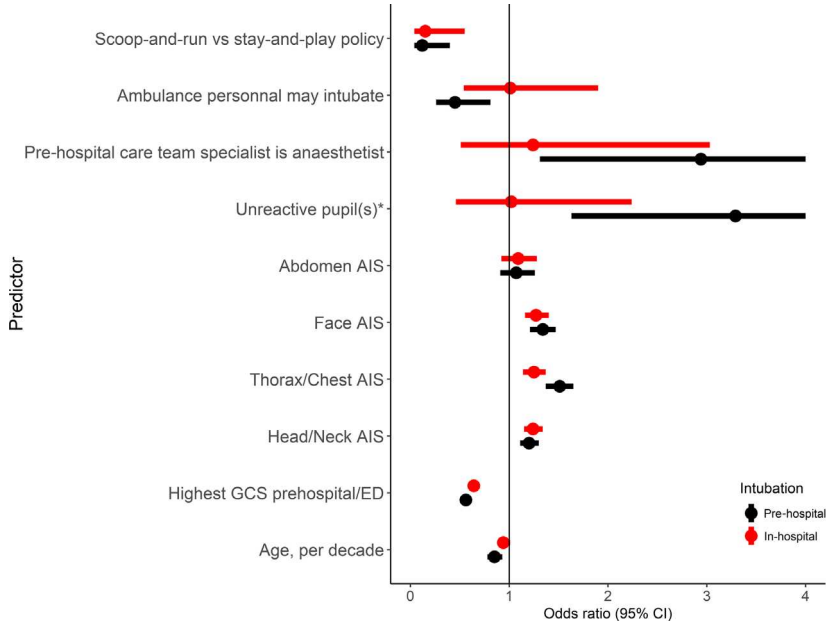


Figure 5 The adjusted effect of the individual predictors on intubation. The results of the full model, including random intercept for centre conditional on country is presented. * pre-hospital assessment. AIS, abbreviated injury score; GCS, Glasgow coma score; ED, emergency department.

This was confirmed by observing large variations between countries and centres. Since this variation was corrected for patient and trauma characteristics, it is more likely the result of guidelines based on low-quality evidence. In general, it is uncertain if not adhering to guidelines with low quality of evidence represents bad clinical practice; in common with the effectiveness of parachutes in preventing death after jumping from an airplane, the absence of evidence does not imply that current practice is problematic [37]. For intubation, however, it has been suggested that low adherence rates with guidelines do affect the outcome of patients [22].

The variation in intubation practice does offer an eloquent solution, since it enables us to identify best clinical practice by comparing regions [24, 38]. This will possibly improve the evidence base regarding intubation, and eventually improve adherence. Moreover, more personalised identification of TBI patients requiring tracheal intubation could be investigated using this method.

Missing data, especially from the pre-hospital scene, was a substantial problem in our study. We dealt with this by focusing on the well-documented factors, and otherwise using multiple imputation, a method proven to give valid estimates under the missing-at-random assumption [32]. It is in the nature of this logistically challenging study that non-observation of data can probably be attributed to random non-administration of data. This mechanism at least does not result in a missing not-at-random pattern. Since we found substantial correlation between variables and sufficient observed auxiliary variables, imputation is likely to be successful. Additionally, it is reassuring that the complete case analysis of the main model showed similar magnitude and direction of the coefficients.

Furthermore, there may have been unmeasured policy characteristics that explain variations in the incidence of tracheal intubation. Even though the thorough development of the questionnaires attempted to ensure the completeness of the topics, they still lacked some specific questions of interest for this analysis. For example, we were not able to assess the following: whether the physician was in favour of intubation when neurological deterioration was anticipated (based on clinical insight); whether the physician was in favour of intubation in patients with mild TBI, or in which cases of mild TBI; or whether intubation occurred to facilitate safe treatment and transfer after TBI in cases of severe agitation, even though the airway may have been uncompromised.

Finally, not all data which we would have wanted for this analysis were registered in the CENTER-TBI database. First of all, it was not possible to distinguish whether patients had their tracheas intubated using rapid sequence induction (RSI) of anaesthesia, or without drugs. Since RSI was the preferred method for intubation in trauma patients who were not moribund, patients who underwent RSI are likely to be different from patients who underwent tracheal intubation without drugs. By not distinguishing between the two, we might have missed some subtle differences in variation. Secondly, we did not document the pre-hospital respiratory rate and oxygen saturation. These are likely to have influenced the decision to intubate, and therefore could have been included as a predictor in the models. Future studies should focus specifically on these aspects to provide additional insights.

However, our study was based on a large sample size and with few exclusion criteria in the analysis. This suggests a high degree of generalisability of our findings.

Although the GCS is the main driver of tracheal intubation, other patient and trauma characteristics, such as injury severity and neurological impairment, play a role in the decision as well. Furthermore, unexplained differences are substantial between countries and between centres. It remains unclear which patients benefit most from tracheal intubation, and further studies are needed to improve the evidence base in TBI patients.

Acknowledgements

We thank G. de Jonge, Biomedical Information Specialist, from the Erasmus MC library, for her help with the literature search. This work was supported by the European Union 7th Framework Program (EC grant 602150). Additional funding was obtained from the Hannelore Kohl Stiftung (Germany), the OneMind (USA) and the Integra LifeSciences Corporation (USA). The funders had no role in the study design, enrolment, collection of data, writing or publication decisions.

References

1. Maas AIR, Menon DK, Adelson PD, et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. *Lancet Neurology* 2017; **16**: 987–1048.
2. Majdan M, Plancikova D, Brazinova A, et al. Epidemiology of traumatic brain injuries in Europe: a cross-sectional analysis. *Lancet Public Health* 2016; **1**: e76–83.
3. Advanced Trauma Life Support. 9th edn.
4. Green RS, Butler MB, Erdogan M. Increased mortality in trauma patients who develop postintubation hypotension. *Journal of Trauma and Acute Care Surgery* 2017; **83**: 569–74.
5. Manley G, Knudson MM, Morabito D, Damron S, Erickson V, Pitts L. Hypotension, hypoxia, and head injury: frequency, duration, and consequences. *Archives of Surgery* 2001; **136**: 1118–23.
6. Boidin MP. Airway patency in the unconscious patient. *British Journal of Anaesthesia* 1985; **57**: 306–10.
7. Moulton C, Pennycook A, Makower R. Relation between Glasgow coma scale and the gag reflex. *British Medical Journal* 1991; **303**: 1240–1.
8. Lockey DJ, Coats T, Parr MJA. Aspiration in severe trauma: a prospective study. *Anaesthesia* 1999; **54**: 1097–8.
9. Atkinson JL. The neglected prehospital phase of head injury: apnea and catecholamine surge. *Mayo Clinic Proceedings* 2000; **75**: 37–47.
10. Carney N, Totten AM, Hawryluk GWJ, et al. *Guidelines for the Management of Severe Traumatic Brain Injury*, 4th ed. Palo Alto, CA: Brain Trauma Foundation, 2016. https://www.braintrauma.org/uploads/13/06/Guidelines_for_Management_of_Severe_TBI_4th_Edition.pdf (accessed 12/08/2019).
11. Badjatia N, Carney N, Crocco TJ, et al. Guidelines for prehospital management of traumatic brain injury. *Prehospital Emergency Care* 2008; **12**: S1–52.

12. Shafi S, Gentilello L. Pre-hospital endotracheal intubation and positive pressure ventilation is associated with hypotension and decreased survival in hypovolemic trauma patients: an analysis of the National Trauma Data Bank. *Journal of Trauma* 2005; **59**: 1140–5.
13. Burney RG, Winn R. Increased cerbrospinal fluid pressure during laryngoscopy and intubation for induction of anesthesia. *Anesthesia and Analgesia* 1975; **54**: 687–90.
14. Davis DP, Meade W, Sise MJ, et al. Both hypoxemia and extreme hyperoxemia may be detrimental in patients with severe traumatic brain injury. *Journal of Neurotrauma* 2009; **26**: 2217–23.
15. Davis DP, Dunford JV, Poste JC, et al. The impact of hypoxia and hyperventilation on outcome after paramedic rapid sequence intubation of severely head-injured patients. *Journal of Trauma* 2004; **57**: 1–10.
16. Marmarou A, Anderson RL, Ward JD, et al. Impact of ICP instability and hypotension on outcome in patients with severe head trauma. *Journal of Neurosurgery* 1991; **75**: S59–66.
17. Stocchetti N, Maas AIR. Traumatic intracranial hypertension. *New England Journal of Medicine* 2014; **370**: 2121–30.
18. Dinsmore J. Traumatic brain injury: an evidence-based review of management. *Continuing Education in Anaesthesia Critical Care and Pain* 2013; **13**: 189–95.
19. Hoffmann M, Czorlich P, Lehmann W, Spiro AS, Rueger JM, Lefering R. The impact of prehospital intubation with and without sedation on outcome in trauma patients with a GCS of 8 or less. *Journal of Neurosurgical Anesthesiology* 2017; **29**: 161–7.
20. Bernard SA, Nguyen V, Cameron P, et al. Prehospital rapid sequence intubation improves functional outcome for patients with severe traumatic brain injury. *Annals of Surgery* 2010; **252**: 959–65.
21. Cnossen MC, Scholten AC, Lingsma HF, et al. Adherence to guidelines in adult patients with traumatic brain injury: a living systematic review. *Journal of Neurotrauma* 2016; **33**: 1–14. https://doi.org/10.1089/neu.2015.4121
22. Franschman G, Peerdeman SM, Greuters S, et al. Prehospital endotracheal intubation in patients with severe traumatic brain injury: guidelines versus reality. *Resuscitation* 2009; **80**: 1147–51.
23. von Elm E, Altman DG, Egger M, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *British Medical Journal* 2007; **335**: 806–8.
24. Maas AIR, Menon DK, Steyerberg EW, et al. Collaborative European neurotrauma effectiveness research in traumatic brain injury (CENTER-TBI): a prospective longitudinal observational study. *Neurosurgery* 2015; **76**: 67–80.
25. Cnossen MC, Polinder S, Lingsma HF, et al. Variation in structure and process of care in traumatic brain injury: provider profiles of European Neurotrauma Centers participating in the CENTER-TBI study. *PLoS ONE* 2016; **11**: 1–21.
26. Foks KA, Cnossen MC, Dippel DWJ, et al. Management of mild traumatic brain injury at the emergency department and hospital admission in Europe: a survey of 71 neurotrauma centers participating in the CENTER-TBI Study. *Journal of Neurotrauma* 2017; **34**: 2529–35.
27. Cnossen MC, van den Brande R, Lingsma H, Polinder S, Lecky F, Maas A. Prehospital trauma care among 68 European neurotrauma centers: Results of the CENTER-TBI Provider Profiling Questionnaires. *Journal of Neurotrauma* 2018; **36**: 176–181. https://doi.org/10.1089/neu.2018.5712
28. van Buuren S. *Flexible imputation of missing data*. Boca Roton, FL: CRC Press, 2018.
29. von Hippel PT. 4. Regression with missing Ys: an improved strategy for analyzing multiply imputed data. *Sociological Methodology* 2007; **37**: 83–117.
30. Nagelkerke NJD. A note on a general definition of the coefficient of determination. *Biometrika* 1991; **78**: 691–2.
31. Merlo J, Chaix B, Yang M, Lynch J, Råstam L. A brief conceptual tutorial on multilevel analysis in social epidemiology: interpreting neighbourhood differences and the effect of neighbourhood characteristics on individual health. *Journal of Epidemiology and Community Health* 2005; **59**: 1022–8.
32. Little RJA, Rubin DB. Statistical analysis with missing data. *Journal of Educational Statistics* 1991; **16**: 150.
33. Li B, Lingsma HF, Steyerberg EW, Lesaffre E. Logistic random effects regression models: a comparison of statistical packages for binary and ordinal outcomes. *BMC Medical Research Methodology* 2011; **11**: 77. https://doi.org/77: 10.1186/1471-2288-11-77
34. Mauritz W, Lingsma HF, Nieboer D, Majdan M, Steyerberg EW, Rusnak M. Glasgow Coma Scale motor score and pupillary reaction to predict six-month mortality in patients with traumatic brain injury: comparison of field and admission assessment. *Journal of Neurotrauma* 2015; **32**: 101–8.
35. Bossers SM, Schwarte LA, Loer SA, Twisk JWR, Boer C, Schober P. Experience in prehospital endotracheal intubation significantly influences mortality of patients with severe traumatic brain injury: a systematic review and meta-analysis. *PLoS ONE* 2015; **10**: e0141034.
36. Buis ML, Maissan IM, Hoeks SE, Klimek M, Stolker RJ. Defining the learning curve for endotracheal intubation using direct laryngoscopy: a systematic review. *Resuscitation* 2016; **99**: 63–71.
37. Smith GCS, Pell JP. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. *British Medical Journal* 2003; **327**: 1459–61.
38. Institute of Medicine. *Initial national priorities for comparative effectiveness research*. Washington, DC: National Academies Press, 2009.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. The three multinomial regression models for intubation.

Table S2. The complete case analysis for intubation, as a sensitivity analysis.

Table S3. The results of the sensitivity analysis not including patients intubated in the referring hospital.

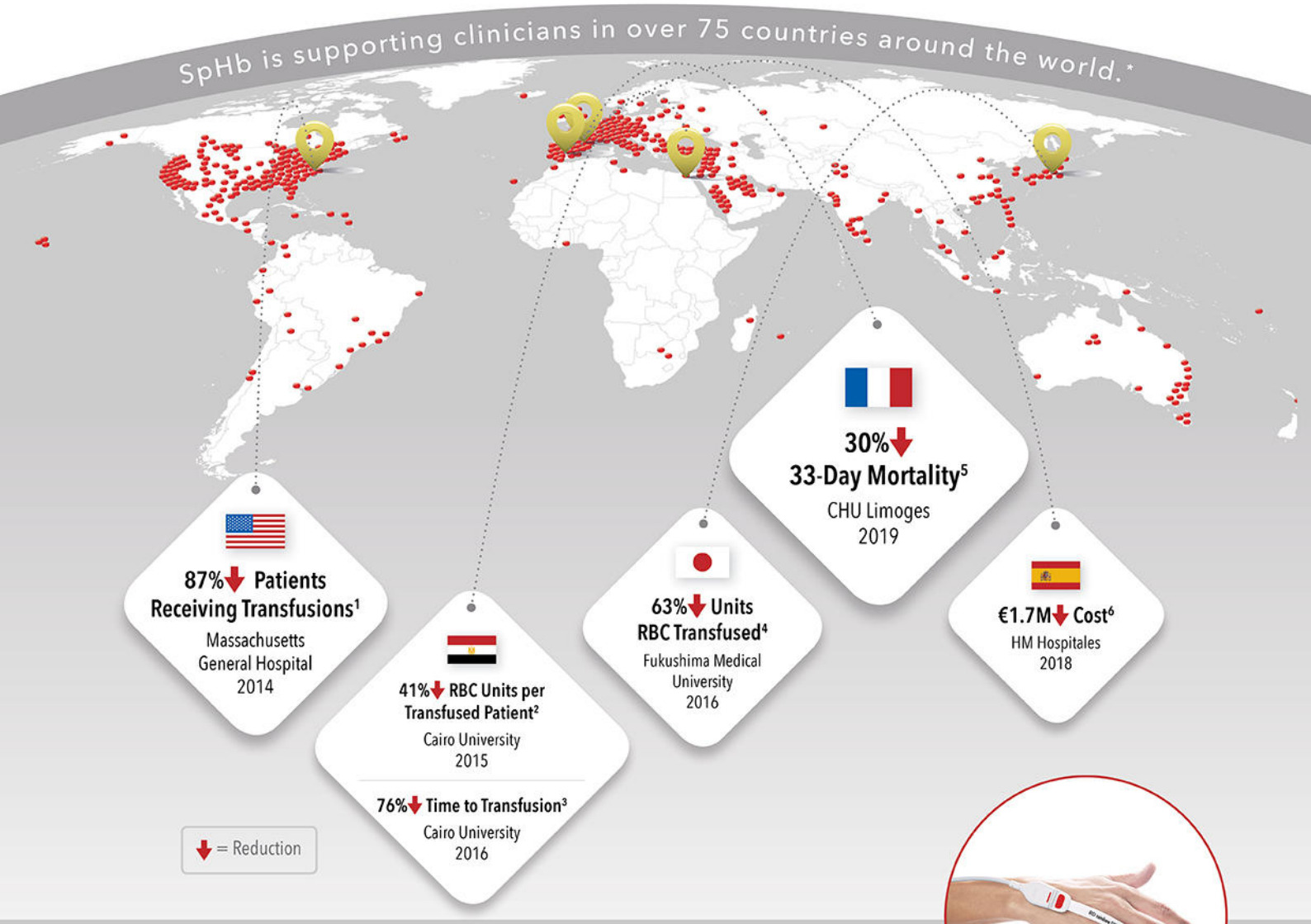
Appendix S1. The CENTER-TBI collaborators

Patient monitoring partner
PHILIPS

Masimo

Are You Improving Outcomes with SpHb®?

Six studies across four continents have found that noninvasive and continuous haemoglobin (SpHb) monitoring can help improve outcomes[1-6]



Improve Your Outcomes with SpHb

Visit www.masimo.co.uk/sphb

For professional use. See instructions for use for full prescribing information, including indications, contraindications, warnings, and precautions.

Clinical decisions regarding red blood cell transfusions should be based on the clinician's judgment considering among other factors: patient condition, continuous SpHb monitoring, and laboratory diagnostic tests using blood samples. SpHb monitoring is not intended to replace laboratory blood testing. Blood samples should be analysed by laboratory instruments prior to clinical decision making.

[1] Ehrenfeld et al. *J Blood Disorders Transf.* 2014. 5:9. [2] Awada WN et al. *J Clin Monit Comput.* DOI 10.1007/s10877-015-9660-4. Study Protocol: In each group, if researchers noted SpHb trended downward below 10 g/dL, a red blood cell transfusion was started and continued until SpHb trended upward above 10 g/dL. The transfusion threshold of 10 g/dL was predetermined by the study protocol and may not be appropriate for all patients. Blood sampling was the same for the control and test group. Arterial blood was drawn from a 20 gauge radial artery cannula into 2 mL EDTA collection tubes, mixed and sent for analysis by a Coulter GEN·S Hematology Analyzer. [3] Kamal A, et al. *Open J of Anesth.* 2016 Mar; 6, 13-19. [4] Imaizumi et al. *Proceedings from the 16th World Congress of Anaesthesiologists* Hong Kong. Abstract #PR607. [5] Cros et al. *J Clin Monit Comput.* Aug 2019: 1-9. Study utilised a goal-directed fluid therapy protocol with PVi® in conjunction with a blood transfusion protocol based on SpHb. [6] Ribed-Sánchez B, et al. *Sensors* (Basel). 2018 Apr 27;18(5). pii: E1367. Estimated national savings derived from hospital savings extrapolated nationwide. * Data on file.

PLCO-003239/PLMM-11257A-1019
PLLT-10899B