Effect of a sedation and ventilator liberation protocol vs usual care on duration of invasive mechanical ventilation in pediatric intensive care units: a randomized clinical trial

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Key points

Question: Does a ventilator liberation intervention reduce duration of invasive mechanical ventilation in children anticipated to require prolonged ventilation in comparison with a non-protocolized approach?

Findings: In this stepped-wedge cluster randomized trial that included 8843 children anticipated to have prolonged ventilation, the unadjusted median time to successful extubation between those receiving protocolized care compared with usual care was 64.8 vs 66.2, respectively. This difference was statistically significant, but smaller than had been anticipated.

Meaning: Among children anticipated to have prolonged ventilation, a ventilation liberation intervention resulted in a reduction in time to first successful extubation; however, the clinical importance of the effect size is uncertain.

Abstract

Importance

There is limited evidence on the optimal strategy for liberating children from invasive mechanical ventilation in the pediatric intensive care unit.

Objective

To determine if a ventilator liberation intervention reduces duration of invasive mechanical ventilation in children anticipated to require prolonged mechanical ventilation.

Design, Setting, Participants

A pragmatic multi-center, stepped-wedge, cluster randomized trial. Seventeen hospital sites (18 pediatric intensive care units) in the United Kingdom were sequentially randomized from usual care to the intervention. From February 2018 to October 2019, 8843 critically ill children anticipated to require prolonged mechanical ventilation were recruited. The last date of follow-up was November 11, 2019.

Interventions

Pediatric intensive care units provided usual care (n = 4155 participants) or the sedation and ventilator liberation intervention (n = 4688 participants) that consisted of assessment of sedation level, daily screening for readiness to undertake a spontaneous breathing trial, a spontaneous breathing trial to test ventilator liberation potential, and daily rounds to review sedation and readiness screening and set patient-relevant targets.

Main outcomes and measures

The primary outcome was duration of invasive mechanical ventilation from initiation of ventilation until first successful extubation. The primary estimate of the treatment effect was a calendar time and cluster adjusted hazard ratio (aHR) with 95% confidence intervals (CI) in children anticipated to have prolonged mechanical ventilation.

Results

All 8843 children observed under intervention and usual care conditions (median age, 8 months; 42% female) completed the trial. The intervention compared with usual care resulted in a significantly shorter median time to successful extubation (64.8 vs 66.2, adjusted median [IQR] difference, -6.1 hours, [-8.2- -5.3]; aHR 1.11, 95% CI 1.02-1.20, *P*=0.02). Serious adverse events included hypoxia (intervention n=9, 0.2% vs usual care n=11, 0.3%) and nonvascular device dislodgement (intervention n=2, 0.04% vs usual care n=7, 0.1%).

Conclusions and relevance

Among children anticipated to have prolonged of mechanical ventilation, a sedation and ventilator liberation intervention compared with usual care resulted in a statistically significant reduction in time to first successful extubation. However, the clinical importance of the effect size is uncertain.

Trial registration

International Standard Randomised Controlled Trial Number ISRCTN16998143

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Introduction

The majority of children admitted to pediatric intensive care units (ICUs) require invasive mechanical ventilation (IMV).[1-4] Despite its benefits, IMV is associated with complications, including ventilator-associated pneumonia and ventilation-induced lung injury. Mechanical ventilation also requires sedation, which likewise is associated with complications that may prolong liberation from IMV.[5]

Weaning protocols are widely used in adult ICUs. The practice of testing readiness for liberation with a spontaneous breathing trial (SBT) is well-established.[6] A meta-analysis of protocolized weaning (14 trials, 2205 participants) reported moderate certainty of evidence for a 26% (95% CI: 13 to 37%) reduction in IMV duration, with 11 trials evaluating the SBT.[7] A systematic review of protocolized weaning in children (3 trials, n=321 participants) concluded that evidence was insufficient to determine net benefit or harm.[8]

Across the UK, there is variation in pediatric ICU sedation and ventilator weaning practices, and minimal involvement of junior medical and nursing clinicians.[9] Furthermore, approximately two thirds of nurses employed in UK pediatric ICUs are junior staff nurses.[4] It was hypothesized that engagement of the existing multiprofessional ICU team in a sedation and ventilation liberation intervention would reduce time to successful liberation from IMV.

Methods

Trial design and oversight

This was a pragmatic, stepped-wedge cluster randomized trial (eFigure 1, **Supplement 1**)[10] with a cost-effectiveness and a process evaluation that will be reported separately. The pragmatic domains are shown in eFigure 2, **Supplement 1**. The National East Midlands Research Ethics Committee

approved the protocol (17/EM/0301, 12 September 2017). An opt-out consent approach was used with distribution of study leaflets to parents and no requirement for written or oral informed consent The Northern Ireland Clinical Trials Unit managed the trial. Data collection was managed through the mandatory national registry of pediatric ICU admissions: the Paediatric Intensive Care and Audit Network (PICANet) [4] with additional items recorded on an electronic case report form. Independent oversight was provided through Trial Steering and Data Monitoring Committees convened by the UK National Institute of Health Research. The protocol was published[11] and the protocol and statistical analysis plan are available in **Supplement 2**.

The primary objective was to determine the effect of the intervention on the duration of IMV in children anticipated to have prolonged IMV. Prolonged IMV was defined *a priori* and determined by diagnostic codes. Diagnostic codes associated with duration of IMV less than 24-hours were categorised as 'short'. All other codes were categorised as 'prolonged'. (e-Methods, **Supplement 1**). As a secondary objective, we determined the effect of the intervention on the duration of IMV for all children irrespective of the prolonged or not categorisation.

Trial sites and participants

All UK hospital sites with one or more pediatric ICUs were eligible for the trial. Children (< 16-years) were eligible if they received IMV and excluded if admitted with a tracheostomy *insitu*, were not immediately expected to survive, were expected to undergo treatment withdrawal, or parents/guardians opted out.

Randomization

The cluster (hospital site) was the unit of randomization. One cluster contained two pediatric ICUs that were randomized together to prevent intervention contamination. All clusters started data

collection simultaneously. At each 4-week period, starting from period three to 18, one cluster transitioned to training and subsequently continued in the intervention condition. The transition order was randomly determined using a computer-generated algorithm and restricted to try to ensure the trial was balanced across control and intervention conditions with respect to the cluster size (large/small) determined by published numbers of ICU admissions .[12] (eMethods, **Supplement 1**)

Interventions and intervention training

A description of the intervention is provided in eMethods in **Supplement 1** and the training resources are available on the website.[13] The intervention incorporated education and training for the multi-professional pediatric ICU team to deliver four key components. Components included assessment of sedation levels using COMFORT scales, daily screening for readiness to undertake a SBT, initiation of a SBT when screening criteria were satisfied and a daily multi-professional round (**Box**). Intervention training included online and face-to-face education. The trial implementation manager trained the local research team and multi-professional champions to roll out training. The intervention was delivered to all children receiving invasive mechanical ventilation in the ICU.

Adherence was measured by the proportion of (a) the four intervention components performed and captured daily; (b) staff trained by end of the transition period; and (c) intervention reach[14] (admissions screened divided by IMV admissions over the trial period). The mean adherence proportions for each ICU were ranked and divided into tertiles.

Usual care is described elsewhere.[9] Typically, this was medically-led, involved a slow reduction in ventilator support to very low levels of support prior to extubation, and ICUs did not have ventilation or sedation protocols. Usual care in participating ICUs at the start of the trial is shown in eTable 1 (**Supplement 1**).

Outcome measures

The primary outcome was the duration of IMV, defined as time from initiation of ventilation until the first successful extubation. Success was defined as still breathing spontaneously for 48-hours after extubation. Pre-specified secondary outcomes as defined in the trial protocol are reported, except cost per complication avoided at 28-days that will be reported elsewhere. Outcomes were measured from patient admission up to 90-days or PICU discharge (whichever was earlier). At the end of the enrolment period, data collection continued for a maximum of 28-days.

Statistical analysis

The planned sample was between 11 024 to 14 310 patients (dependent on the intra-cluster correlation coefficient, ICC). Following the internal pilot, re-estimation of the mean duration of IMV was 5.8 (SD 9.6) days and ICC 0.005 (95% CI: 0.001 to 0.01). A revised sample size calculation estimated that 9520 patient admissions would provide 80% to 87% power to detect a 1-day target effect size. The one-day difference was considered by the study team as clinically important and plausible for patients managed with a ventilation liberation intervention following discussions with ICU staff during pre-trial feasibility work. Sample size calculations assumed a simple exchangeable correlation structure as was the convention at the time.[15]

ICUs were analyzed according to the sequence they were randomized to, so all participants were analyzed according to their randomized group. In this way, ICUs were assumed exposed to the intervention following their training periods. Patients admitted during training periods were not included. For the primary analysis, observations with missing outcome data were excluded and for the secondary analysis, adjusting for individual level covariates, observations with missing outcome or covariate data were excluded. Missing data were minimal and there was no requirement for multiple imputation. The proportion of missing data for the primary analysis for the primary outcome was 0.17%, and 0.18% for the secondary adjusted analysis. The primary estimate of the

198 treatment effect was a time and cluster adjusted hazard ratio (aHR) with 95% CIs. A 2-sided P < .05
199 significance threshold was used for all analyses. Because of the potential for type 1 error due to
200 multiple comparisons, findings for analyses of secondary endpoints should be interpreted as
201 exploratory.

202 For the primary and time-to-event secondary outcomes, Cox proportional hazards models were used
203 with a frailty term for clustering by ICU (which accounts for random cluster effects). Time-to-event
204 outcomes were censored at the point of transitioning from the usual care condition to the training
205 periods, discharge to another hospital, at 90-days, death, and point of receiving a tracheostomy.
206 Checks of the appropriateness of the proportional hazards assumption indicated no evident
207 departures from proportionality on Schoenfeld residuals plots. For time to event outcomes, an
208 absolute measure of effect was derived by computing the median of the model-based prediction of
209 survival duration at all 22 time periods, for both the intervention and usual care conditions, and the
210 difference between the two; and summarising the extent of variability using the inter-quartile range
211 over the 22 time periods.

212 Binary secondary outcomes were analysed using mixed effects binomial regression with a log-link to
213 estimate the adjusted relative risk (aRR); and a binomial model with identity link to estimate the
214 adjusted risk difference (aRD), with estimation using the restricted maximum likelihood approach.
215 All mixed models included cluster as a random effect assuming an exchangeable correlation
216 structure and used the Kenward and Roger small sample correction [16] to correct the potential
217 inflation of the type I error rate due to small number of clusters. In the case of non-convergence of
218 binomial linear mixed models to estimate risk differences, marginal estimates of risk differences
219 using generalised estimating equations, assuming an independent correlation structure, with a Fay
220 and Graubard small sample correction on standard errors, with 95% confidence intervals derived
221 from a z-distribution were reported. [17] In the case of non-convergence of the binomial model with a
222 log-link, a Poisson model with robust standard errors was fitted. For continuous outcomes, similar

models were used with an identity link and assuming a normal distribution, but checking for normality assumptions and making transformations where necessary.

A pre-specified secondary analysis of the primary outcome was conducted adjusting for additional covariates: age, severity of illness (PIM3 score), respiratory versus other diagnostic grouping, type of admission (planned/unplanned), and reason for admission (surgical/medical). A pre-specified exploratory subgroup analysis was conducted for the primary outcome using a global test for interaction and 99% CI for size of unit (large and small, based on annual admissions); adherence to the intervention (tertiles of ranked averages); type of admission to unit (planned and unplanned); and reason for admission (surgical, medical respiratory, and medical other). To assess sensitivity to assumptions made about the nature of time effects and correlations an extensive series of sensitivity analyses for the secondary binary outcomes was conducted (e-Methods, **Supplement 1**). This showed very little difference between the more complex correlation structures and the exchangeable correlation structures that were assumed in the primary analysis (**Supplement 3**).

Analyses were conducted using Stata®/SE Versions 16.1 (StataCorp LP, College Station, TX, USA) and SAS software, version 9.4 (SAS Institute). Variance components (ICCs) are reported.

Results

Trial sites and participants

All 18 ICUs opened simultaneously to recruitment on 5 February 2018 and closed on 14 October 2019. The last date of follow-up was 11 November 2019. Participating ICUs had a greater number of beds, annual patient admissions and included more London sites than non-participating ICUs (eTable 2, **Supplement 1**). The trial included 10 495 admissions, of which 8843 were in diagnostic groups identified as anticipated to require 'prolonged' ventilation (**Figure 1).** Patient characteristics were

well balanced across intervention and usual care conditions (**Table 1;** all children eTable 3, **Supplement 1**).

Delivery of the intervention

A total of 1865 of 2247 (median 85%, IQR: 80%, 90%) eligible clinical staff completed training within the 8-week training period and by 12-weeks the total completed was 1955 (median 88%, IQR: 80%, 90%) (eTable 4, **Supplement 1**). Across ICUs, adherence was high for intervention reach (median 82%, IQR 77%, 89%), sedation assessment (median 83%, IQR 82%, 91%), setting targets for sedation level (median 85%, IQR 63%, 89%) and ventilation parameters (median 90%, IQR 81%, 96%). Adherence was moderate for SBT screening (median 74%, IQR 66%, 83%) and lower for proceeding to SBT when screening criteria were met (median 40%, IQR 31%, 51%). (eTable 5, **Supplement 1**). Documented reasons for non-progression to SBT and extubation are summarized in eTables 6 and 7, **Supplement 1**.

Primary outcome

After adjustment for cluster and calendar time, the intervention resulted in a significantly shorter duration of IMV before successful extubation (aHR for extubation 1.11, 95% CI 1.02 to 1.20, *P*=0.02). The median (IQR) hours was 64.8 (22.1-141.4) in the intervention condition compared with 66.2 (21.8-138.0) in usual care and the adjusted median (IQR) difference across all calendar time periods was -6.1 (-8.2- -5.3) hours **(Table 2;** all children eTable 8, **Supplement 1**). The probability and time to successful extubation by observation period is shown in **Figure 2** (all children, eFigure 3, **Supplement 1**).

In a prespecified secondary analysis that adjusted for additional covariates, the findings were not statistically significant (prolonged ventilation cohort, aHR 1.07, 95% CI 0.98 to 1.16, P=0.13; all children, aHR 1.06, 95% CI 0.98 to 1.14, P=0.17).

Secondary outcomes

There was a significantly higher incidence of successful extubation in the intervention condition (aRR 1.01, 95% CI 1.00-1.02, *P*=0.03). There was no significant difference in total duration of IMV (median (IQR) days, intervention, 2.7 (0.9-6.3) vs usual care, 2.8 (0.9-5.9); adjusted median (IQR) -0.20 (-0.25--0.18); aHR 1.09, 95% CI 1.00-1.18, *P*=0.06). Post-extubation use of non-invasive ventilation was significantly higher in the intervention condition (aRR 1.22, 95% CI 1.01-1.49, *P*=0.04), but there was no significant difference in duration of non-invasive ventilation (median (IQR) days, intervention, 1.8 (0.7-6.8) vs usual care, 2.1 (0.7-6.6); adjusted median (IQR) 0.22 (0.18-0.29); aHR 0.9, 95% CI 0.7-1.2, P=0.43). ICU length of stay was not significantly different (median (IQR) days, intervention, 5.0 (3.0-10.0) vs usual care, 5.0 (3.0-9.0); adjusted median (IQR) difference 0.00 (0.00-0.00); aHR 0.97, 95% CI 0.90-1.06, *P*=0.53), but there was a significantly longer hospital length of stay in the intervention condition (median (IQR) days, intervention, 9.6 (5.0-19.8) vs usual care, 9.1 (5.0-18.9); adjusted median (IQR) difference 0.91 (0.84-0.97); aHR 0.89, 95% CI 0.81-0.97, *P*=0.01). The intervention resulted in a significantly higher incidence of unplanned extubation (aRR 1.62, 95% CI 1.05-2.51, *P*=0.03), but no significant differences in reintubation (aRR 1.10, 95% CI 0.89-1.36, *P*=0.38) (**Table 2**; all children eTable 8, **Supplement 1**).

In relation to other safety outcomes, there were no statistically significant differences between intervention or usual care in risk of tracheostomy; post-extubation stridor; or mortality in ICU or hospital for both patient cohorts (**Table 2;** all children eTable 8, **Supplement 1**). Variance components ICC for all secondary binary outcomes are reported in eTable 9, **Supplement 1**.

Adverse events

There were 18 and 25 serious adverse events in the intervention and usual care conditions respectively. Events included hypoxia (intervention n=9, 0.2%; usual care n=11, 0.3%) and nonvascular device dislodgement (intervention n=2, 0.04%); usual care n=7, 0.1 %). (eTable 10; all children eTable 11, **Supplement 1**).

Clinical and Exploratory outcomes

Baseline ventilation parameters were similar (eTable 12, **Supplement 1**). Ventilation parameters immediately before the SBT in the intervention condition and 2-hours before extubation in usual care were not different in any clinically important extent (eTable 13, **Supplement 1**).

Exploratory subgroup analyses for the duration of IMV before successful extubation showed no significant interactions in pre-specified subgroups based on size of unit, type of admission, reason for admission and adherence to the intervention (eFigure 4, **Supplement 1**).

Discussion

In this stepped-wedge cluster randomized clinical trial in children anticipated to require prolonged ventilation, the use of a sedation and ventilation liberation intervention compared with usual care significantly reduced the duration of IMV to successful extubation. The effect size was small and thus the clinical significance is uncertain. The significant effect was consistent across all children receiving mechanical ventilation.

The small effect may have resulted from several factors. First, the trial recruited a broad population and as a result, there may have been heterogeneity in the treatment effect that could have

attenuated the overall effect. As a result, a greater effect in a more focused population cannot be excluded. Second, given the historic lack of bedside nurses' involvement in ventilator weaning in the UK[9], engaging the nurses fully in the process may have prompted earlier consideration of extubation; this was a key factor in a previous study.[18] Third, observations showed a lower adherence to undertaking a SBT when screening criteria were satisfied and may reflect clinician hesitancy to drop swiftly from a high to a low level of support to test readiness for liberation. While the screening criteria indicated potential to proceed to a SBT, progression may not have been clinically inappropriate. Reluctance and non-adherence may plausibly be a sign of the difficulties clinicians experience in changing long-standing practices.[19] Further, the large numbers of staff required to deliver the trial intervention may have attenuated the effect compared to the effect size seen in other smaller pediatric trials evaluating a SBT as a ventilation liberation intervention.

Very few pediatric randomized clinical trials have specifically evaluated a daily screening and SBT strategy. In a two-center trial recruiting mainly medical patients, Foronda et al reported a reduction in duration of IMV of more than 24 hours in the SBT group (n=294, median 3.5 versus 4.7 days, P=0.01).[20] A single-site trial of cardiac surgical patients by Ferreira et al reported a significant reduction in extubation success in the SBT group (n=110, 83% versus 68%, p = 0.02), but a longer difference in duration of IMV in the SBT group that did not meet statistical significance (median 29.4 versus 21.5 hours, P=0.29).[21] In both trials, relatively few clinicians delivered the intervention in a controlled manner; thus, the findings may not directly translate when applied into wider clinical practice. In contrast, Curley et al evaluated a sedation protocol incorporating am SBT delivered by each site's multidisciplinary team in a 31-site cluster trial that enrolled medical patients.[5] They reported no significant differences in duration of IMV between groups (n=2449, both groups median 6.5 days), but showed reduced variation in sedation management with inter-professional involvement. In the current study, the median duration of IMV days in usual care was less than three days and much shorter than that reported in other pediatric studies evaluating SBTs[5,20,21] or other weaning protocols.[22-24] It was also shorter than pre-trial estimations that were based on the mean

duration. It is possible that, with a shorter duration of IMV in usual care, the intervention had a reduced absolute effect.

The significantly higher incidence of unplanned extubation may be associated with less sedation and more awake patients. However, the proportion of unplanned extubation was lower than 4 to 8% reported elsewhere,[5,25] and did not result in a higher rate of reintubation. This may be an indication that some patients might be ready to breathe without assistance sooner than previously expected, a point raised in previous adult and pediatric studies.[26,27] Thus in some respects, usual care may be a conservative approach. The greater use of non-invasive ventilation after extubation in the intervention condition may reflect the need for continued ventilator support because of earlier extubation. Alternatively, it could also reflect clinician discomfort with a more accelerated weaning and extubation approach in contrast to a conservative approach.

Children in the intervention condition had a significantly longer hospital stay. Whether this finding represents an association with the intervention or is a consequence of greater use of non-invasive ventilation or other factors cannot be ascertained within the present study.

The stepped-wedge design had several strengths. It helped overcome the risk of intervention contamination in usual care; maximise power to detect an effect; facilitate intervention training; and increase ICU participation by guaranteeing receipt of the intervention.[28] The pragmatic recruitment facilitated testing in a broader population that would potentially benefit from the intervention.

Limitations

This study has several limitations. First, assignment of the intervention was unblinded. This may have led to performance or detection bias. Second, hospital sites were the unit of randomization, and the children enrolled were a heterogeneous group with a variety of respiratory, cardiac, and other impairments. Whether the intervention would perform differently in a more homogenous group

remains to be determined. Third, the intervention included several components and adherence to all components was not uniformly observed. It was not possible to determine which components were primarily responsible for the observed effect. Fourth, data on sedatives, analgesics and sedation levels were not collected; rather ICU teams were recommended to consider the child's sedation needs informed by COMFORT scores and SBT readiness screens. Fifth, the categorization of diagnostic codes to define prolonged ventilation was based on diagnoses that typically require more than 24-hours of ventilation. Stratification based on codes requiring more prolonged ventilation (e.g. more than 48 hours) may have shown different effects.

Conclusions

Among children anticipated to have prolonged of mechanical ventilation, a sedation and ventilator liberation intervention compared with usual care resulted in a statistically significant reduction in time to first successful extubation. However, the clinical importance of the effect size is uncertain.

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Dr Bronagh Blackwood and Ms Cliona McDowell had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES

1. Balcells Ramírez J, López-Herce Cid J, Modesto Alapont V. [Prevalence of mechanical ventilation in pediatric intensive care units in Spain]. *An Pediatr (Barc).* 2004;61(6):533-541.
2. Wolfler A, Calderoni E, Ottonello G, et al. Daily practice of mechanical ventilation in Italian pediatric intensive care units: a prospective survey. *Pediatr Crit Care Med.* 2011;12(2):141-146.
3. Farias JA, Fernández A, Monteverde E, et al. Mechanical ventilation in pediatric intensive care units during the season for acute lower respiratory infection: a multicenter study. *Pediatr Crit Care Med.* 2012;13(2):158-164.
4. PICANet. Paediatric Intensive Care Audit Network (PICANet) 2019 Annual Report. https://www.picanet.org.uk/annual-reporting-and-publications/ Published 2019. Accessed 16 July, 2020.
5. Curley MA, Wypij D, Watson RS, et al. Protocolized sedation vs usual care in pediatric patients mechanically ventilated for acute respiratory failure: a randomized clinical trial. *Jama.* 2015;313(4):379-389.
6. Burns KEA, Raptis S, Nisenbaum R, et al. International Practice Variation in Weaning Critically Ill Adults from Invasive Mechanical Ventilation. *Annals of the American Thoracic Society.* 2018;15(4):494-502.
7. Blackwood B, Burns KE, Cardwell CR, O'Halloran P. Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients. *Cochrane Database Syst Rev.* 2014;2014(11):Cd006904.
8. Blackwood B, Murray M, Chisakuta A, Cardwell CR, O'Halloran P. Protocolized versus non-protocolized weaning for reducing the duration of invasive mechanical ventilation in critically ill paediatric patients. *Cochrane Database Syst Rev.* 2013;2013(7):Cd009082.
9. Blackwood B, Tume L. The implausibility of 'usual care' in an open system: sedation and weaning practices in Paediatric Intensive Care Units (PICUs) in the United Kingdom (UK). *Trials.* 2015;16:325.
10. Blackwood B. PRagmatic-Explanatory Continuum Indicator Summary (PRECIS-2) for the SANDWICH trial. http://www.precis-2.org/Trials. Published 2021. Accessed 1 February 2021.
11. Blackwood B, Agus A, Boyle R, et al. Sedation AND Weaning In Children (SANDWICH): protocol for a cluster randomised stepped wedge trial. *BMJ Open.* 2019;9(11):e031630.
12. Ivers NM, Halperin IJ, Barnsley J, et al. Allocation techniques for balance at baseline in cluster randomized trials: a methodological review. *Trials.* 2012;13:120.
13. McIlmurray L. SANDWICH: Sedation and Weaning in Children. Queen's University Belfast. https://www.qub.ac.uk/sites/sandwich/. Accessed 1 December, 2020.
14. Moore GF, Audrey S, Barker M, et al. Process evaluation of complex interventions: Medical Research Council guidance. *Bmj.* 2015;350:h1258.
15. Hemming K, Kasza J, Hooper R, Forbes A, Taljaard M. A tutorial on sample size calculation for multiple-period cluster randomized parallel, cross-over and stepped-wedge trials using the Shiny CRT Calculator. *Int J Epidemiol.* 2020;49(3):979-995.
16. Leyrat C, Morgan KE, Leurent B, Kahan BC. Cluster randomized trials with a small number of clusters: which analyses should be used? *Int J Epidemiol.* 2018;47(3):1012.
17. Thompson JA, Hemming K, Forbes A, Fielding K, Hayes R. Comparison of small-sample standard-error corrections for generalised estimating equations in stepped wedge cluster randomised trials with a binary outcome: A simulation study. *Stat Methods Med Res.* 2020:962280220958735.
18. Ely EW, Baker AM, Evans GW, Haponik EF. The prognostic significance of passing a daily screen of weaning parameters. *Intensive Care Med.* 1999;25(6):581-587.
19. Gupta DM, Boland RJ, Jr., Aron DC. The physician's experience of changing clinical practice: a struggle to unlearn. *Implement Sci.* 2017;12(1):28-28.

20. Foronda FK, Troster EJ, Farias JA, et al. The impact of daily evaluation and spontaneous breathing test on the duration of pediatric mechanical ventilation: a randomized controlled trial. *Crit Care Med.* 2011;39(11):2526-2533.
21. Ferreira FV, Sugo EK, Aragon DC, Carmona F, Carlotti A. Spontaneous Breathing Trial for Prediction of Extubation Success in Pediatric Patients Following Congenital Heart Surgery: A Randomized Controlled Trial. *Pediatr Crit Care Med.* 2019;20(10):940-946.
22. Schultz TR, Lin RJ, Watzman HM, et al. Weaning children from mechanical ventilation: a prospective randomized trial of protocol-directed versus physician-directed weaning. *Respir Care.* 2001;46(8):772-782.
23. Randolph AG, Wypij D, Venkataraman ST, et al. Effect of mechanical ventilator weaning protocols on respiratory outcomes in infants and children: a randomized controlled trial. *Jama.* 2002;288(20):2561-2568.
24. Jouvet PA, Payen V, Gauvin F, Emeriaud G, Lacroix J. Weaning children from mechanical ventilation with a computer-driven protocol: a pilot trial. *Intensive Care Med.* 2013;39(5):919-925.
25. Baisch SD, Wheeler WB, Kurachek SC, Cornfield DN. Extubation failure in pediatric intensive care incidence and outcomes. *Pediatr Crit Care Med.* 2005;6(3):312-318.
26. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet.* 2008;371(9607):126-134.
27. Kurachek SC, Newth CJ, Quasney MW, et al. Extubation failure in pediatric intensive care: a multiple-center study of risk factors and outcomes. *Crit Care Med.* 2003;31(11):2657-2664.
28. Hemming K, Taljaard M. Reflection on modern methods: when is a stepped-wedge cluster randomized trial a good study design choice? *Int J Epidemiol.* 2020;49(3):1043-1052.

Box. Components of the intervention
Assessment of sedation levels by the bedside nurse using the COMFORT[a] score (every 6-hours as a minimum time interval)
Assessment of readiness to undertake a SBT by the bedside nurse using screening criteria (minimum twice daily) FiO2 ≤ 0.45 SpO2 ≥ 95% (or as appropriate) PEEP ≤ 8cm H_2O PIP ≤ 22cm H_2O Cough present
A spontaneous breathing trial to assess readiness for ventilator. Decision to begin taken by a nurse or doctor with the appropriate experience and authority; conducted and monitored by bedside nurse (up to maximum 2-hours) Spontaneous breathing mode (CPAP) PEEP 5cm H_2O Pressure Support 5cmH_2O (above PEEP)
Multidisciplinary round reviewing the child's COMFORT scores and spontaneous breathing trial assessments with feedback to the bedside nurse on sedation level and ventilation parameter targets (minimum daily)

564 Abbreviations: CPAP, continuous positive airway pressure; FiO2, fraction of inspired oxygen; PEEP,
565 positive end-expiratory pressure; PIP, peak inspiratory pressure

566 [a] The COMFORT scale assesses pain and sedation to determine if the child is adequately comfortable

567 or in need of more or less medication to keep them ventilated.

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Table 1. Baseline Characteristics of Patient Admissions and Pediatric Intensive Care Units

Patient Characteristics	**Intervention Condition (n = 4688)**	**Usual Care (n = 4155)**
Female, No. (%)	1970 (42.0)	1744 (42.0)
Male, No. (%)	2716 (57.9)	2410 (58.0)
Age on admission, median (IQR), months	7 (1-45)	9 (1-47)
No. (%)		

Less than 1 month	1042 (22.2)	772 (18.6)
1 to less than 24 months	2077 (44.3)	1937 (46.6)
24 to less than 72 months	710 (15.2)	665 (16.0)
72 months or greater	859 (18.3)	780 (18.8))
Previous ICU admission, No. (%)	1429 (30.5)	1102 (26.5)
Pediatric Index of Mortality 3[a], median (IQR)	0.02 (0.01-0.05)	0.02 (0.01-0.05)
Primary diagnostic group, No. (%)		
Cardiovascular	1613 (34.4)	1226 (29.5)
Respiratory	1410 (30.1)	1289 (31.0)
Other	602 (12.8)	484 (11.7)
Neurological	385 (8.2)	431 (10.4)
Gastroenterology	316 (6.7)	294 (7.1)
Infection	253 (5.4)	307 (7.4)
Oncology	109 (2.3)	124 (3.0)
Type of admission, No. (%)		
Medical, unplanned	2659 (56.7)	2624 (63.2)
Medical, planned	265 (5.7)	153 (3.7)
Post-surgical, planned	1532 (32.7)	1128 (27.2)
Post-surgical, unplanned	232 (5.0)	250 (6.0)

Pediatric Intensive Care Unit Characteristics (n = 18)	
Beds, No. (%)	
6 to 11	9 (50)
12 to 30	9 (50)
Fellowship training provision, No. (%)	15 (72.2)
Intensivist coverage, No. (%)	18 (100)
Unit type, No. (%)	
General	11 (61.1)
General and cardiac mixed	5 (27.8)

Cardiac	2 (11.1)
Sedation assessment validated tool in place prior to study[b], No. (%)	13 (72.2)
Sedation protocol in place prior to study[c], No. (%)	4 (22.2)
Ventilation weaning protocol in place prior to study[d], No. (%)	3 (16.7)

[a] Paediatric Index of Mortality 3 (PIM3) is a predictive model based on ten explanatory variables collected at the time of admission to intensive care to estimate the probability of death. Reporting an index ranging from 0 to 1, the higher the index, the higher the estimated probability of death.
[b] Sedation assessment tools in place were either COMFORT original or COMFORT behavioural which were used in the intervention (see footnote a in box).
[c] Sedation protocols in place prescribed the reduction of sedatives, whereas the intervention recommended that sedatives were adjusted to achieve a COMFORT range (see footnote a in box).
[d] Weaning protocols in place prescribed stepwise reductions in ventilator support, whereas the intervention prescribed daily screening and a spontaneous breathing trial

Note for production:
The ICU characteristics can be placed in the left-hand column and the right remain empty if needed to maintain a three-column format.

Table 2. Outcomes

	Observation period		Adjusted analyses[a]			
	Intervention Condition (n = 4688)	Usual Care (n = 4155)	Absolute Scale		Relative Scale	
	Median (IQR) hours		Median Difference (IQR) hours[b]	P value	Hazard Ratio (95%CI)	P value
Primary Outcome						
Duration of invasive mechanical ventilation until 1st successful extubation[c]	64.8 (22.1-141.4) (n=4684)	66.2 (21.8-138.0) (n=4144)	-6.1 (-8.2- -5.3)	0.02	1.1 (1.0-1.2)	0.02
	Median (IQR) days		Median Difference (IQR) days[b]	P value	Hazard Ratio (95%CI)	P value
Secondary Outcomes						
Total duration of invasive mechanical ventilation[c]	2.7 (0.9-6.3) (n=4684)	2.8 (0.9-5.9) (n=4144)	-0.20 (-0.25- -0.18)	0.06	1.09 (1.00-1.18)	0.06
Duration post-extubation non-invasive ventilation[c]	1.8 (0.7-6.8) (n=805)	2.1 (0.7-6.6) (n=556)	0.22 (0.18-0.29)	0.43	0.91 (0.72-1.15)	0.43
Pediatric ICU length of stay	5.0 (3.0-10.0) (n=4688)	5.0 (3.0-9.0) (n=4155)	0.00 (0.00-0.00)	0.53	0.97 (0.90-1.06)	0.53
Hospital length of stay	9.6 (5.0-19.8) (n=4010)	9.1 (5.0-18.9) (n=3581)	0.91 (0.84-0.97)	0.01	0.89 (0.81-0.97)	0.01
	N (%)		% Point Difference (95% CI)		Relative Risk (95% CI)[d]	
Successful extubation [e]	4161 (98.6) (n=4222)	3788 (98.4) (n=3849)	0.95(-0.07-1.97)	0.07	1.01 (1.00-1.02)	0.03
Unplanned extubation	142 (3.0) (n=4688)	107 (2.6) (n=4155)	0.98(-0.32-2.27)	0.14	1.62 (1.05-2.51)	0.03
Reintubation [f]	544 (11.6) (n=4688)	507 (12.2) (n=4155)	0.83(-1.70-3.37)	0.52	1.10 (0.89-1.36)	0.38
Post-extubation non-invasive ventilation	810 (18.9) (n=4285)	558 (14.4) (n=3886)	9.42(4.30-14.54)	<0.001	1.22 (1.01-1.49)	0.04
Tracheostomy[g, h]	46 (1.0) (n=4688)	33 (0.8) (n=4155)	-0.03(-0.49-0.43)	0.89	0.88 (0.36-2.17)	0.79
Post-extubation stridor[i]	419 (8.9) (n=4688)	356 (8.6) (n=4155)	3.05(-1.71-7.80)	0.21	0.94 (0.73-1.22)	0.66
Pediatric ICU mortality	220 (4.7) (n=4682)	173 (4.2) (n=4154)	0.25(-1.98-2.49)	0.82	1.06 (0.73-1.54)	0.75
Hospital mortality[j]	268 (6.3) (n=4278)	200 (5.3) (n=3785)	0.82(-1.96-3.61)	0.56	1.15 (0.82-1.63)	0.41

Footnotes:

[a] All outcomes were adjusted for cluster (pediatric ICU) and calendar time (period categorical effect).

[b] Adjusted median differences and IQR were calculated across the 22 time periods

[c] Time-to-event outcomes were censored at the point of transitioning from usual care to the training period, discharge to another hospital, at 90-days, death, and point of receiving a tracheostomy.

[d] The Poisson regression with robust standard errors (to correct for misspecification of Poisson distribution for binomial distribution) was used to estimate the relative risk

[e] Percentage successful extubations in patients where extubation was attempted. An extubation that did not require reintubation within a 48-hour time period was considered successful.

[f] Percentage point difference estimated using a mixed effects binomial model with identity link. All other outcomes, percentage point difference was estimated using generalised estimating equations

[g] Due to lack of convergence, marginal estimates of risk difference were developed without using a small sample correction

[h] During the study period

[i] Laryngeal edema resulting in stridor upon extubation

[j] Includes ICU mortality

Figure title and legends

Figure 1. Selection of pediatric intensive care units and enrolment of patients in a stepped-wedge cluster randomized trial of a sedation and ventilator liberation intervention in children

[a] 1 hospital site had 2 pediatric ICUs that were randomized together to avoid contamination of the intervention
[b] 3 patients excluded from analysis, could not link to PICANet data set
[c] diagnostic codes associated with a short duration of ventilation (<24 hours) were categorized as 'short', all others were categorized as 'prolonged'.

Figure 2. Kaplan Meier. Probability and time to successful extubation by observation period in the prolonged invasive ventilation cohort

Footnote: The hazard ratio and the median difference (IQR) were adjusted for cluster and calendar time. Patients were observed from initiation of ventilation until the first successful extubation (defined as still breathing spontaneously for 48-hours after extubation). The curves on the graph are created using the adjusted figures. The risk table presents the absolute patient numbers and therefore will not match precisely.