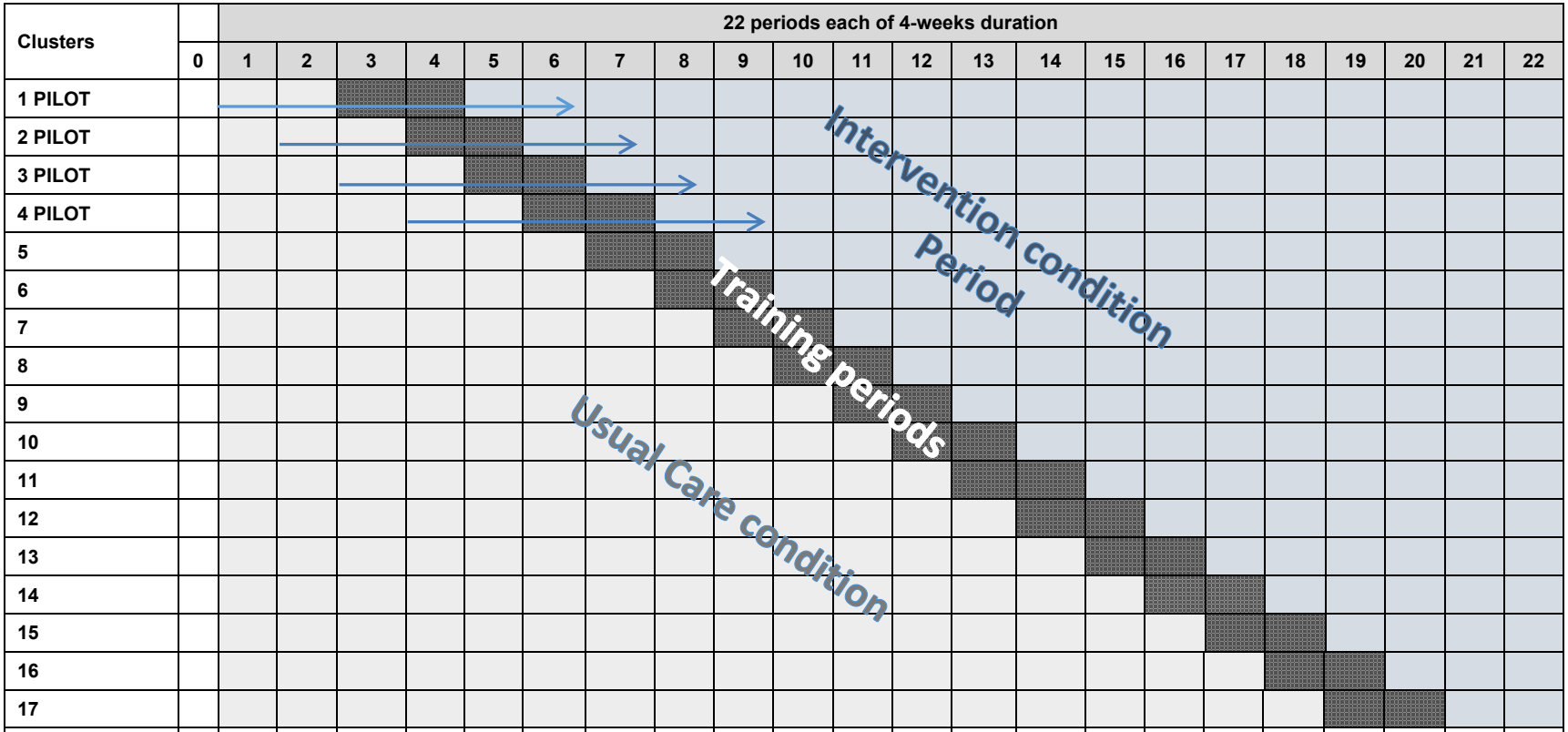
Supplemental Online Content

Blackwood B, Tume LN, Morris KP, et al; for the SANDWICH Collaborators. 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. *JAMA*. doi:10.1001/jama.2021.10296

This supplemental material has been provided by the authors to give readers additional information about their work.

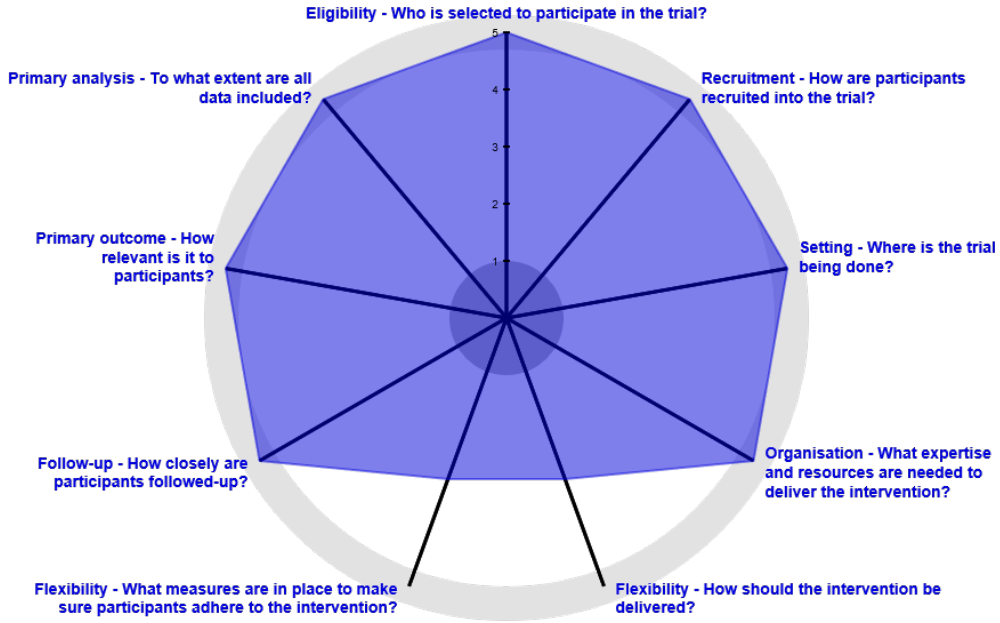
eFigure 1. Study schematic



This cluster included two ICUs Each shaded column represents a 4-week period. The shaded cells represent the control condition (light) and the intervention condition (dark). The patterned cells represent the transition to the two training periods during which recruitment was suspended. Recruitment re-commenced when the ICU transitioned to the intervention condition. The internal pilot was conducted in the first four clusters that were randomized to transition to the intervention. In the two periods before, during and after training, data were collected on recruitment, opt-out, training targets, adherence to intervention components and feasibility of data collection procedures to assess progression. The decision to progress was made by the Trial Steering Committee and the NIHR

Health Technology Assessment programme. The internal pilot continued without interruption into the trial. Importantly no outcome data from the internal pilot was considered in determining the decision to progress and there was no change in the trial protocol between the internal pilot and the overall trial.

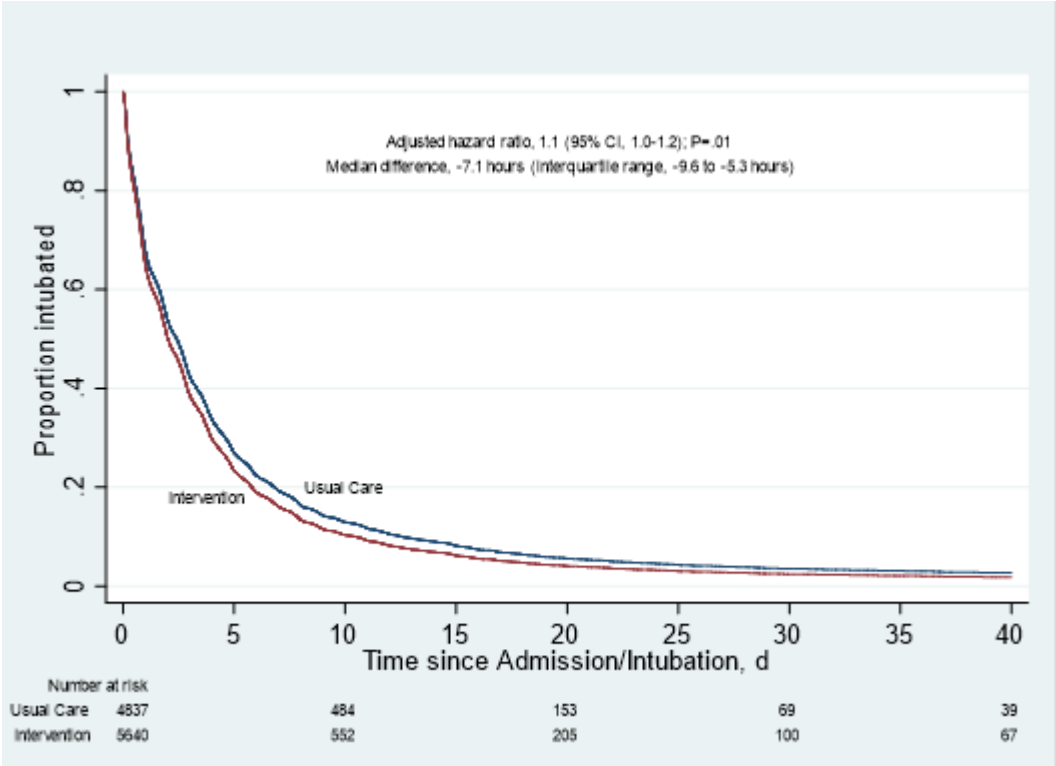
eFigure 2. PRagmatic-Explanatory Continuum Indicator Summary (PRECIS-2)[10]



The 9 domains of trial design are scored from 1 (very explanatory, designed to demonstrate efficacy in “ideal conditions”) to 5 (very pragmatic, designed to assess effectiveness in “usual conditions”). The blue shading represents the design scores, demonstrating that the trial design is closer to pragmatic than explanatory. Explanation for the SANDWICH scores are below.

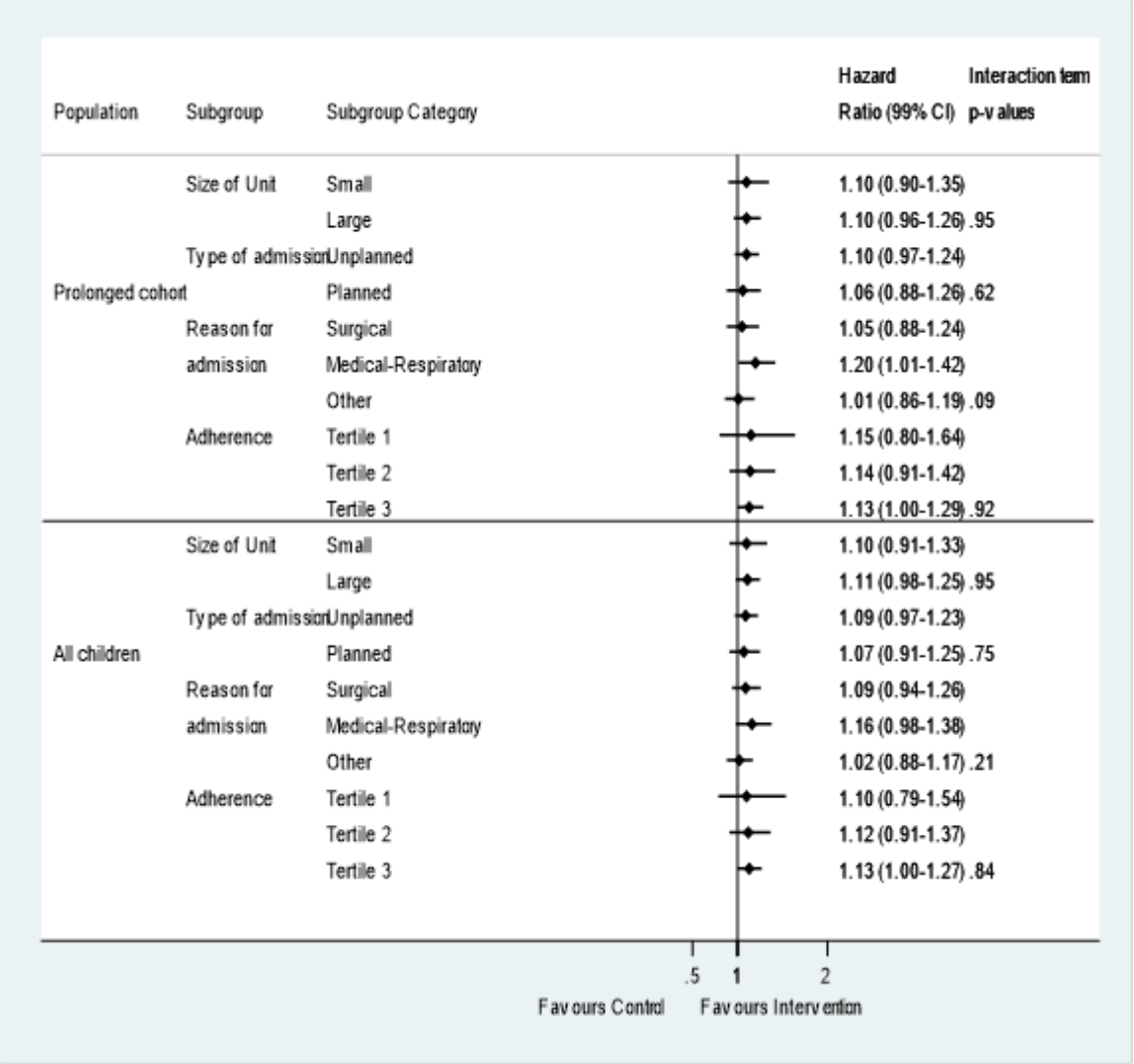
Explanation for the SANDWICH trial PRECIS-2 domain scores
Eligibility: All children who were intubated and mechanically ventilated were eligible unless there was a reason that they would not be extubated
Recruitment: All children meeting eligibility in participating pediatric ICUs were recruited
Setting: Within the UK. 18 out of a total of 28 pediatric ICUs in the UK participated
Organisation: The intervention could be slotted into the usual organisation of care for mechanically ventilated children making use of no more than the existing healthcare staff and resources in that setting.
Flexibility, intervention delivery: Sedation assessment was delivered as per usual care, flexible in timing but with a minimum of 6-hourly assessment. Daily screening was delivered as prescribed by the protocol which was new to staff. A SBT was also prescribed and new to staff, although there was flexibility in clinically decisions about whether or not to proceed. The ward round was usual care, but added was the requirement to set targets for sedation levels and ventilation that were appropriate for the child and were fed back to the bedside nurse.
Flexibility, adherence: Fidelity to the intervention was measured. Feedback on adherence was fed back to the ICU at intervals to encourage greater adherence. There were no sanctions for non-adherence.
Follow-up: All data were available electronically by medical records and the national registry for pediatric ICUs.
Primary outcome: Highly relevant confirmed in pre-trial work with parents and young people groups.
Primary analysis: There were very few missing data on outcomes.

eFigure 3. Probability and time to successful extubation by observation period in all children



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 with the covariate adjusted curve

eFigure 4. Subgroup analyses for time to successful extubation



eMethods

Additional information on categorization of short and prolonged ventilation groups

Primarily, this pragmatic study was commissioned to address ventilator liberation in any child who could potentially benefit from earlier weaning. We deemed a one-day difference to be clinically important, so children with conditions that typically required less than one-day ventilation were less likely to benefit. We were careful not to define prolonged duration of IMV in terms of hours (as duration was the primary outcome). Thus, *a priori*, we defined prolonged as those children with diagnoses that typically required longer than 24-hours IMV. The definition and selection of prolonged cases was data-driven from the Paediatric and Intensive Care Audit Network (PICANet) database; a mandatory registry for pediatric ICU designation.[1]

Using historical PICANet data (accessed 30 Oct 2018), diagnostic codes associated with a short duration of IMV (24 hours or less) were identified and categorised as 'short'. Admissions that did not include a short diagnostic code were anticipated to have prolonged IMV and were categorised as 'prolonged'.

In total, there were 35,105 codes associated with a short ventilation time. They were classified into 11 categories.

1. Allergic reactions
2. Atrial septal defect
3. Atrial surgery/Mitral valve surgery
4. Aortic coarctation
5. Epilepsy
6. Fracture
7. Musculoskeletal surgery
8. Poisoning; drug overdose
9. Pulmonary vein abnormality
10. Scoliosis
11. Ventricular septal defect (isolated repair)

Due to the large number of diagnostic codes, it was not feasible to list diagnostic exclusions in the eligibility assessment for the study, therefore all children requiring IMV were included and subsequent analyses were conducted on both the 'prolonged' IMV cohort and all children

The SANDWICH intervention

We used the template for intervention description and replication (TIDieR) checklist and guide to describe the intervention and aid replicability of the intervention and its delivery in practice[2].

Item 1. Name of the intervention

The name of the intervention was 'sedation and weaning in children, a coordinated care protocol' that was more informally known as the SANDWICH intervention.

Item 2. Why: Describe any rationale, theory, or goal of the elements essential to the intervention

Sedation and weaning are inextricably linked and clinical coordination of care is an important priority, therefore it made sense to package these components together in a way that was not overly complicated: (a) daily evaluation of readiness for liberation incorporating a SBT; (b) sedation assessment and a strategy to minimise sedation; and (c) maximisation of engagement of staff. While the individual components have been evaluated separately, the evidence is limited due to the paucity of paediatric trials, and they have not been combined and evaluated in this particular way.

Item 3. What (materials): Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (for example, online appendix, URL)

Materials are provided in the SANDWICH website https://www.qub.ac.uk/sites/sandwich/.

Item 4. What (procedures): Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities

The intervention incorporated co-ordinated care among the ICU multiprofessional team with greater nursing involvement in the sedation and ventilation weaning process. Formerly, bedside nurses had no formal involvement in the weaning process.[3] The intervention comprised four key components.

1. Sedation assessment

Minimum 6-hourly assessment of sedation using one of two COMFORT tools undertaken by bedside nurses. The COMFORT Original has 8 score categories each scored between 1 and 5 based on behavioural and physiological values observed on the child. The total score is derived from adding each of the category scores resulting in a range from 8-40. During regular ward round review of sedation, the target range of scores within which the COMFORT score should lie were agreed according to the child's progress (e.g. during acute phase 13-17 range; during weaning phase 18-25 range) [4].

The COMFORT Behavioural has 6 score categories each scored between 1 and 5 based on behaviours exhibited by the child. The total score is derived from adding each of the category scores resulting in a range from 6-30. During regular ward round review of sedation, the target range of scores within which the COMFORT B score should lie were agreed according to the child's progress (e.g. during acute phase 10-12 range; during weaning phase 12-17 range) [5].

2. Readiness for a spontaneous breathing trial (SBT)

This component was conducted twice-daily. Five clinical parameters were assessed to test the child's readiness for a SBT. The assessment was generally conducted by the bedside nurse and included the following:

- $FiO_2 \leq 0.45$
- $SpO_2 \geq 95\%$ (or as appropriate to underlying condition)

- positive end expiratory pressure (PEEP) ≤ 8cm H_2O
- peak inspiratory pressure (PIP) ≤ 22cm H_2O
- Cough present

When criteria were met, the nurse was instructed to stop or reduce sedation (as determined during the ward round) and inform a senior clinician (medical or nursing) that the child was potentially ready to undertake a 2-hour SBT. The decision to proceed was judged by the senior clinician.

3. Spontaneous breathing trial

If the senior clinician decided to proceed with the SBT, ventilator support was reduced to a PEEP of 5cmH_2O and a pressure support of 5cmH_2O (above PEEP).

During the SBT, the bedside nurse monitored the child for signs of respiratory distress:

- A 20% increase in heart or respiratory rate (above pre-SBT rates),
- Signs of increased work of breathing (use of accessory muscles, asynchronous breathing)
- SpO_2 < 92% or significant sustained increase in FiO_2 requirement

If the SBT was deemed successful (i.e. breathing spontaneously with no distress within the 2-hour trial), progression to extubation was discussed with medical staff.

4. Ward round clinical assessment

The multiprofessional clinical ward round was designed to facilitate greater inter-professional collaboration. It included nursing and medical disciplines, and others such as physiotherapy, pharmacy and dieticians according to usual practice in the ICU. Rounding provided the clinical team the opportunity to review patients' sedation management including the sedation assessment COMFORT scores, the sedative regimen and setting sedation targets. In addition, regular clinical review of the child's ventilation status was undertaken and ventilation goals were set. Daily sedation and ventilation targets were be fed back to the child's bedside nurse and recorded on the daily bedside record.

Enabling and support activities

The SANDWICH education package

Creating an education package to train critical care staff to deliver each element of the intervention was a major focus of the study. The education package was created by the clinical research team with specialist support from an established NHS online education provider (LearnPro NHS: http://www.learnpro.co.uk) and a medical film-maker from Temple St Hospital, Dublin, Ireland.

Online course

The on-line course included inbuilt assessment of learning against objectives. It enabled tracking of staff training completion at the ICU level: this facilitated monitoring and feedback to trainers/researchers during the training and intervention periods. This approach was used successfully by co-applicant Walsh in the DESIST trial[6] in adult ICUs, to achieve >80% training completion within 2-3 months by nursing staff for a sedation-analgesia education package.

The course consisted of seven modules, four addressed the components of the intervention and two provided background education on the evidence underpinning protocolised weaning, optimum sedation management and pharmacology of the sedative and analgesic drugs commonly used in ICU. The topics covered included:

1. Why get sedation right?
2. Pharmacology of commonly used sedative drugs
3. COMFORT B *[5]
4. COMFORT Original *[4]
5. Multidisciplinary ward round

6. Bedside screen for SBT readiness

7. Spontaneous breathing trials

* The e-learning module had two pathways to facilitate use of either COMFORT version.

Staff completed an assessment at the end of each four essential component modules. A score ≥80% was required in each module to obtain a training certificate.

SANDWICH manual

A detailed education manual was compiled to complement the online training; this included a PowerPoint slide set and training folder. Materials were designed using the same palette of fonts and colours, and included photographs, graphics and colourful diagrams. The manual comprised 136 pages, with sections on instructions for accessing the online e-learning course; face-to-face teaching resources including alternative teaching formats; standard operating procedures for training and assessment; and training logs. The manual was given to the ICU principle investigator and champion team on the first day of onsite training delivered by the implementation manager.

Item 5. Who provided: For each category of intervention provider (for example, psychologist, nursing assistant), describe their expertise, background and any specific training given

Intervention trainers

Implementation manager: an implementation manager was specifically funded by the trial to support and manage intervention training for local trainers over the course of the trial. The manager was a senior paediatric critical care registered nurse with 10 years pediatric ICU experience. She held a BSc in Nursing, MPhil and Postgraduate Higher Diploma in Paediatric Critical Care Nursing. Pediatric ICU trainers and SANDWICH champions: all trainers and champions were local ICU staff with current critical care expertise. They included:

- Clinical educators
- Critical care nurses (various grades)
- Critical care doctors (registrar to consultant level)
- Advanced nurse practitioners (ANP)
- Physiotherapists
- SANDWICH research nurses

Each individual received the full training from the implementation manager, and had responsibility for rolling out the full training or aspects of the training to other staff.

Intervention providers

All clinical staff within the ICU were the intervention providers. These included:

- Critical care nurses (all grades)
- Critical care doctors (all grades)
- Advanced nurse practitioners (ANP)
- Physiotherapists

Some staff had greater involvement in particular components. The ward round had multidisciplinary involvement of doctors, nurses and relevant other disciplines. There were generally two models of ward round: the bedside or in a separate room in the ICU. If conducted at the bedside, the bedside nurses would be included; if conducted in a separate room, a senior nurse would feedback relevant sedation and ventilation issues to and from the bedside nurse to the ward round attendees. COMFORT sedation assessment, readiness for SBT screening and conducting a SBT were generally undertaken by bedside nurses. However, decisions around sedation and ventilation target setting and proceeding to conduct a SBT or to extubate afterwards were generally

undertaken by senior medical staff or ANPs. The procedure for extubation was undertaken following standard unit procedure and was not prescribed in the SANDWICH protocol.

Item 6. How: Describe the modes of delivery (such as face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group

The SANDWICH intervention was delivered using a multi-faceted approach that included both on-line and face-to-face engagement (both individually and in groups). On-line education was delivered using an established NHS online education provider (LearnPro NHS: http://www.learnpro.co.uk). The on-line module provided training in the protocol and the underpinning clinical evidence supporting protocolised weaning. Video footage on COMFORT assessment was obtained by permission from Professor van Dijk (http://www.comfortassessment.nl/web/). The module included an inbuilt assessment of learning against objectives, and also enable training completion at ICU level to be tracked and fed back to local educators / researchers during the training and intervention periods. Face-to-face training was delivered by the implementation manager, ICU trainers, champions and the SANDWICH research nurses.

Item 7. Where: Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features

The intervention was delivered within UK pediatric ICUs. Training was delivered within ICUs either at the bedside or in training rooms within the ICU. The intervention involved greater engagement of junior nurses in the weaning processes. Within the UK setting, the term junior nurse refers to nurses within the Band 5 pay grade, but a nurse may be in this band for 5 years. In ICU, it generally includes nurses who do not have the recognised specialised pediatric ICU course, which can be undertaken after 1 to 2 years pediatric ICU experience. This intervention is relevant within an international context; particularly in countries where no such specialised course exists, thus this context is reflective of a wider international context.

Item 8. When and how much: Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose

The intervention training was provided over an 8-week training period, initially to trainers by the implementation manager, thereafter by trainers and champions. This was concentrated in the 8-week period, but was delivered locally with the arrival of new staff. The intervention itself was delivered daily for the duration of the trial after the ICU cross over to the intervention period.

Item 9. Tailoring: If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how

The duration and dose of the intervention components could not be adapted. However, the schedule of timing of ward rounds, readiness for SBT screening and sedation assessment could be personalised to suit the ICU working practices. The ward round could be within a room in the ICU or a bedside walk around at times that suited clinically, but were usually morning and afternoon. Screening could be undertaken by night staff before the end of their shift (i.e. early morning) and by day staff in the morning and afternoon. Screening was generally undertaken at times that enabled sufficient time to deliver a SBT and consider extubation if necessary. Sedation assessment was undertaken 6-hourly at times that coincided with the bedside nurse's assessment practices.

The SBT screening checklists could not be adapted, but could be incorporated into the ICU bedside computer monitoring programme if required.

Item 10. Modifications: If the intervention was modified during the course of the study, describe the changes (what, why, when, and how)

No modifications were made to the intervention during the trial.

Item 11. How well (planned): If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them

Training: target 80% staff trained within 8-week period. Training was assessed both in-house and online. All staff were required to register and complete the online intervention training programme that incorporated assessments. The online programme monitored successful completion of training and assessments and generated progress reports. Within the 8-week training period, progress reports were fed back from the implementation manager to the local ICU research team on the numbers of staff who had completed. Research staff and champions were able to encourage untrained staff to complete training. Staff who successfully completed were provided with a certificate of completion. In-house, the ICU champions supplemented online training by providing face-to-face training. A record log was maintained in each ICU of training provided face-to-face. Progress reports and training logs were retained by the trial team.

Adherence was measured for the following five components of the intervention:

1. minimum* of two COMFORT assessments/day
2. minimum* of one SBT readiness screen
3. daily* ventilation target set
4. daily* sedation target set
5. SBT performed when criteria were met

(* minimum requirements were chosen to capture all adherence, particularly for children admitted to ICU halfway through the day)

Research nurses collected the data on the daily data collection form during the intervention period. The total proportion for the intervention period was reported and the adherence rates were fed back to ICUs via the SANDWICH research nurses.

Adherence to training completion was measured at 8 and 12-weeks after the training period. The data were collected by the LearnPro programme team and numbers trained were reported to the implementation manager. Training rates were fed back to local unit trainers, the local PI and the research nurses at 8 and 12 weeks.

Item 12: How well (actual): If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned

Adherence is reported in the results section (intervention delivery) of the main paper, and accompanied by data in eTables 3, 4 and 5 in this supplement.

Following the report of the internal pilot period, we provided 3-monthly individual unit feedback on intervention adherence to the ICUs in the intervention phase (13 Mar 2019; 10 Jun 2019, 16 Sep 2019). Feedback was presented in a format enabling ICUs to compare their own adherence to that of other ICUs (anonymized) in the intervention phase. Additionally, during the trial's monthly intervention teleconferences (including ICU PIs, SANDWICH research nurses, the CI and research team), ICU teams discussed and shared strategies to enhance adherence.

Model based analysis plan for binary and secondary outcomes including detailed sensitivity analysis

There are a number of requirements for the analysis model for this stepped-wedge cluster randomised trial. Firstly, this is a clustered trial and all analysis will take clustering into account. Secondly, the trial has 17 clusters, and the model will allow for a correction due to the small number of clusters. Thirdly, the design is a stepped-wedge study and we will adjust for temporal confounding. Full details on how each of these will be undertaken, with justification and detailed sensitivity analysis to all underlying assumptions, is provided below for all binary and continuous outcomes[7].

Binary outcomes

A mixed effects binomial regression with a log-link will be used to estimate the relative risk; and a binomial model with identity link used to estimate the risk difference, with estimation using REML. In the case of non-convergence of the binomial model with a log-link, a Poisson model with robust standard errors will be fitted. If the binomial model with the identity link does not converge then only a relative risk will be reported. If neither the log or identity link converge we will use the logistic link and report odds ratios. We will include fixed effects for period and a fixed effect for intervention exposure. The primary analysis will allow for clustering as a random effect assuming an exchangeable correlation structure. To correct the potential inflation of the type I error rate due to small number of clusters, the Kenward and Roger small sample correction will be used. NOTE: on request of editors at JAMA, in the case of non-convergence of binomial linear mixed models to estimate risk differences, we report marginal estimates of risk differences using generalised estimating equations, assuming an independent correlation structure, with a Fay and Graubard small sample correction on standard errors, with 95% confidence intervals derived from a z-distribution.[8]

Continuous outcomes

For continuous outcomes we will report mean differences estimated from mixed effects linear regression with identity link. All continuous outcomes will be checked for normality and appropriate transformations used. All analysis other than choice of link function will take the same form above, including small sample corrections.

Additional sensitivity analyses

In a sensitivity analysis we will explore if models with more complicated correlation structures are a better fit to the data. These models are not being used as our primary analysis models as there is limited understanding as to when such models will converge and how to choose between the various different correlation structures which might be plausible. To this end we will additionally fit generalised linear mixed models (with same link functions and fixed effects as described above) to include the following correlation structures: a block exchangeable correlation structure to include a random cluster and random cluster by period effect; and a discrete time decay correlation structure including a random cluster effect with auto-regressive structure (AR(1)). We will report AIC and log-likelihoods from all models so we can make an informal comparison of goodness of fit. Although there are currently no recommended models to formally compare goodness of fit between different correlation structures, any large differences in goodness of fit between these models should be evident from conventional goodness of fit statistics. Should there be large differences and differences between results (point estimates of treatment effects and confidence intervals, results will be interpreted cautiously).

To additionally explore if the categorical effect for time (i.e. fixed period effect) is both parsimonious and adequate to represent the extent of the secular trend, we will model the time effect using a spline function. The number of knots used here will be taken as the default. Again, for verification of results this model will also be fitted in Stata under the exchangeable correlation structure and without a small sample correction. Models will be extended to include random cluster by intervention effects (with a non-zero covariance term) to examine if results are sensitive to the assumption of no intervention by cluster interaction. Models will also be extended to include an interaction between treatment and number of periods since first treated, to examine if there is any indication of a relationship between duration of exposure to the intervention and outcomes.

Estimation and reporting of within cluster correlations

We will report time adjusted within-cluster correlations for all outcomes. We will report correlations from the different assumed correlation structures (so we will report intra-cluster correlations (ICC); within and between-period correlations; and within-period correlations and exponential decay). As well as reporting correlations we will additionally report all variance components. For all outcomes (continuous and binary) we will report

correlations on the latent scale (i.e. proportions scale for binary outcomes) as is appropriate to inform future sample size calculations. To this end, to estimate the intra-cluster correlations, a linear mixed effects regression model with an identity-link will be fitted, with a random cluster effect and fixed period effect and fixed intervention effect. To report the estimated within-period ICC, between-period ICC assuming a block-exchangeable correlation structure we will fit a linear mixed effects regression model with an identity-link, with a random cluster and random cluster by period effect, and fixed period effect and fixed intervention effect. To report the within-period ICC and the rate of exponential decay under the discrete time decay correlation structure we will fit a linear mixed effects regression model with an identity-link, with a random cluster and auto-regressive structure (AR(1)), and fixed period effect and fixed intervention effect. No small sample corrections will be made when fitting models for intra-cluster correlation estimates as interest here is in the variance components and not the treatment effect.

Implementation

These binary models will be fitted in SAS using proc glimmix because Stata both does not accommodate small sample corrections for binary outcomes and does not accommodate exponential correlation structures. However, binary outcomes will be analysed in Stata without the small sample correction and under the exchangeable correlation structure as a means of verification of results. For continuous outcomes analysis will again be in SAS using proc mixed (hpmixed for exponential decay to improve computational time) in Stata using mixed.

eTable 1. Usual care in participating pediatric ICUs

ICU	Unit type	Beds (N)	Sedation scoring tool	Sedation protocol	Ventilation weaning protocol	ANPs
01	General, cardiac	21	COMFORT B[a]	No	No	Yes
02	General	12	COMFORT O[b]	No	No	No
03	General, cardiac, liver, neurosurgical, ECLS, ENT, oncology, metabolic, spinal	29.5	COMFORT B	No	Yes	Yes
04	General, cardiac	17	COMFORT B	No	Yes	No
05	Cardiac, respiratory	16	COMFORT O	No	No	Yes
06	General	9	COMFORT O	No	No	Yes
07	General	6	COMFORT O	No	No	Yes
08	General, neonatal	26	COMFORT O	No	No	No
09	Cardiac	19	COMFORT O	No	No	Yes
10	General	8	COMFORT B	Yes	No	No
11	General, cardiac	16	COMFORT B	No	No	Yes
12	General	11	Non-validated tool	Yes	No	No
13	General, neurosurgical, craniofacial, major trauma	8	None	No	No	Yes
14	General, cardiac, neurosurgery	14	None	No	No	Yes
15	General, neurosurgical, oncology, surgical	6	COMFORT B	Yes	No	No
16	General	7	Non-validated tool	Yes	No	No
17	General	6.5	None	No	No	No
18	General	9	COMFORT B	No	Yes	Yes

ANPs, advanced nurse practitioners (includes skills in advanced airway management, extubation, prescribing, insertion of invasive devices); ECLS, extra corporeal life support; ECMO, extra corporeal membrane oxygenation
[a] COMFORT Behavioural tool[5]; [b] COMFORT Original tool[4]

Additional information: Sedation assessment was undertaken in the majority of ICUs (15, 83.3%): assessment periods varied. In all ICUs, the ICU consultant (attending) was primarily responsible for ventilator weaning decisions. Typically, weaning involved a slow reduction in ventilator support to very low levels of support prior to extubation. Very few ICUs (3, 16.7%) used a weaning protocol or a sedation protocol (3, 16.7%); no ICUs used both. No formal criteria, or use of SBTs, were used to assess readiness for ventilator liberation. Bedside nurses had no formal role in the weaning process.[3]

eTable 2. Characteristics of UK pediatric ICUs

Pediatric ICU characteristics	Participating ICUs *n (%)* n = 18 (64.3)	Non-participating ICUs *n (%)* n = 10 (35.7)	All UK pediatric ICUs N = 28
Region			
North	4 (14.3)	3 (10.7)	7 (25.0)
Midlands West/East	3 (10.7)	3 (10.7)	6 (21.4)
London	6 (21.4)	2 (7.1)	8 (28.6)
South West/East/Central	3 (10.7)	0	3 (10.7)
Wales[a]	1 (3.6)	0	1 (3.6)
Northern Ireland[a]	1 (3.6)	0	1 (3.6)
Scotland[b]	0	2 (7.1)	2 (7.1)
Type of hospital			
University	18 (64.3)	10 (35.7)	28 (100)
Size of unit (beds)			
<8	4 (14.3)	4 (14.3)	8 (28.6)
8-11	5 (17.9)	2 (7.1)	7 (25.0)
12-15	2 (7.1)	2 (7.1)	4 (14.3)
>/= 16	7 (25.0)	2 (7.1)	9 (32.1)
Annual ICU admissions			
<500	4 (14.3)	6 (21.4)	10 (35.7)
500-749	9 (32.1)	2 (7.1)	11 (39.3)
750-999	4 (14.3)	1 (3.6)	5 (17.9)
>/= 1000	1 (3.6)	1 (3.6)	2 (7.1)

[a] Only one pediatric ICU in this country
[b] Scotland was legally restricted from using opt-out consent

Source https://www.picanet.org.uk/wp-content/uploads/sites/25/2018/11/PICANet-2018-annual-report-summary-v1.1.pdf

eTable 3. Characteristics of all patient admissions at baseline

Characteristic	Intervention Condition	Usual Care
Total no.	5646	4849
Female sex – no. (%)	2426 (43.0)	2048 (42.2)
Male sex – no. (%)	3217 (57.0)	2800 (57.7)
Age at ICU admission median (IQR), months	9 (1, 54)	10.5 (2, 52)
No. (%)		
Less than 1 month	1078 (19.1)	802 (16.5)
1 to less than 24 months	2463 (43.6)	2245 (46.3)
24 to less than 72 months	940 (16.7)	832 (17.2)
72 months or greater	1165 (20.6)	968 (20.0)
Previous ICU admission – no. (%)	1523 (27.0)	1176 (24.2)
Pediatric Index of Mortality 3[a] – median (IQR)	0.02 (0.01-0.05)	0.01 (0.01-0.05)
Primary diagnostic group – no. (%)		
Cardiovascular	2105 (37.3)	1586 (32.7)
Respiratory	1410 (25.0)	1289 (26.6)
Neurological	734 (13.0)	672 (13.9)
Other	713 (12.6)	573 (11.8)
Gastroenterology	316 (5.6)	294 (6.1)
Infection	255 (4.5)	309 (6.4)
Oncology	113 (2.0)	126 (2.6)
Type of admission – no. (%)		
Planned, following surgery	2074 (36.7)	1507 (31.1)
Unplanned, following surgery	244 (4.3)	268 (5.5)
Planned, medical	283 (5.0)	167 (3.4)
Unplanned, medical	3045 (53.9)	2907 (59.9)
Anticipated ventilation trajectory[b] – no. (%)		
Prolonged	4688 (83.0)	4155 (85.7)
Short	958 (17.0)	694 (14.3)

[a] Pediatric 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] children's anticipated ventilation trajectory was defined using historical PICANet data. Diagnostic codes associated with a short duration of invasive ventilation (<24 hours) were identified and categorised as 'short'. Admissions that did not include a short diagnostic code were categorised as 'prolonged'.

eTable 4. Proportion (%) of staff trained within 8 and 12 weeks at each hospital site

Hospital site ID	Total 8-weeks (n)	Trained 8-week (n)	%	Total 12-weeks (n)	Trained 12-weeks (n)	%
S08/09	369	346	94%	372	335	90%
S03	309	183	59%	282	223	79%
S01	213	191	90%	213	192	90%
S04	142	129	91%	142	129	91%
S14	132	114	86%	132	114	86%
S13	115	97	84%	115	103	90%
S18	108	92	85%	111	98	88%
S11	116	96	83%	116	97	84%
S05	108	87	81%	108	87	81%
S02	88	70	80%	88	70	80%
S12	96	83	86%	96	83	86%
S15	82	62	76%	80	70	88%
S06	84	76	90%	96	92	96%
S16	83	68	82%	94	84	89%
S10	78	61	78%	78	68	87%
S07	71	57	80%	71	57	80%
S17	53	53	100%	53	53	100%
Totals	2247	1865	83%	2247	1955	87%

All staff were required to register and complete the online intervention training programme that incorporated assessments. The online programme monitored successful completion of training and assessments and generated progress reports.

eTable 5. Proportion (%) of intervention adherence at each hospital site

Hospital site ID	COMFORT assessed	Target set COMFORT	Target set ventilation	Readiness for SBT assessed	SBT initiated	Training target	Reach*	Average
S16	93.5	98.3	99.1	81.5	54.8	82	88.6	85.4
S17	88.0	92.0	96.0	70.8	60.0	100	82.3	84.2
S18	90.9	93.5	95.9	84.2	53.0	85	74.5	82.4
S15	96.9	96.5	98.4	63.3	51.9	76	76.7	80.0
S02	84.1	89.1	91.6	66.0	48.4	80	92.5	78.8
S01	82.0	87.4	87.3	89.9	21.6	90	88.3	78.1
S13	81.6	89.3	91.8	74.5	38.5	84	86.8	78.1
S08/09	84.7	81.5	89.95	62.6	39.2	94	86.6	76.95
S06	69.8	65.2	95.0	81.0	50.6	90	82.3	76.3
S05	90.7	87.1	81.4	54.0	32.0	81	100.0	75.2
S12	83.1	82.4	82.6	72.5	33.1	86	78.0	74.0
S04	79.3	62.5	88.0	61.3	45.4	91	89.5	73.9
S11	75.8	77.5	73.6	86.8	29.5	83	71.9	71.2
S07	77.5	63.2	96.3	76.1	19.8	80	75.3	69.7
S10	94.0	34.8	34.8	92.5	44.7	78	72.6	64.5
S03	81.8	53.7	56.8	83.4	15.0	59	85.3	62.1
S14	83.2	39.1	28.1	66.8	30.8	86	80.1	59.2

Adherence was measured by capturing whether or not COMFORT was assessed at least twice daily; daily ward round targets were set for sedation and ventilation; readiness for SBT was assessed at least daily; an SBT was initiated when criteria were met; and the proportion of staff trained at the end of the eight week training period.

*Reach, defined as the extent to which a target population came into contact with the intervention[9], was measured by the proportion of patients screened (recruits and exclusions) divided by IMV admission patients (reported by PICANet over the trial period).

eTable 6. Reasons provided for not progressing to conduct a spontaneous breathing trial when the screening criteria were satisfied

Reason	N (%)
Neuromuscular weakness	432 (3.89)
Low consciousness: sedation or neurological	1631 (14.68)
Airway protection reasons: secretion, oedema	2717 (24.45)
High haemodynamic support	1100 (9.90)
Expected return to theatre	1545 (13.90)
Limited staff resources	210 (1.89)
Too late in the evening	351 (3.16)
Other reasons[a]	
Child's condition	650 (5.85)
Awaiting external specialist review	106 (0.95)
Awaiting hospital transfer	56 (0.50)
Long term ventilation or palliative care	47 (0.42)
Self extubated prior to planned SBT	39 (0.39)
Prioritizing weight gain	106 (0.95)
Awaiting further investigation	36 (0.32)
Non-adherence	1072 (9.65)
No reason provided	941 (8.47)
Unobtainable	75 (0.68)
Total	11,114

eTable 7. Reasons provided for not progressing to extubation when the spontaneous trial was successful

Reason	N (%)
Neuromuscular weakness	45 (3.13)
Low consciousness: sedation or neurological	251 (17.47)
Airway protection reasons: secretion, oedema	341 (23.73)
High hemodynamic support	27 (1.88)
Expected return to theatre	177 (12.32)
Limited staff resource	153 (10.65)
Too late in the evening	137 (9.53)
Other reasons[a]	
Child's condition	87 (6.05)
Awaiting external specialist review	25 (1.74)
Awaiting hospital transfer	6 (0.42)
Palliative care	3 (0.21)
Self extubation	3 (0.21)
Awaiting further tests	10 (0.70)
Incomplete fasting period	7 (0.49)
Non-adherence	90 (6.26)
No reason provided	75 (5.22)
Total	1437

[a] Other reasons were provided in free-form text. These reasons were content analysed and categorised by authors LMcI, and LT.

eTable 8. Outcomes for all children

Main Clinical Outcomes	Observation period		Adjusted analyses[a]			
	Intervention (n = 5646)	Usual Care (n = 4849)	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]	51.4 (17.0-123.6) (n=5640)	55.2 (18.0-123.6) (n=4837)	-7.1 (-9.6- -5.3)	0.01	1.1 (1.0-1.2)	0.01
	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]	2.2 (0.7-5.5) (n=5640)	2.4 (0.8-5.5) (n=4837)	-0.28(-0.33- -0.20)	0.03	1.09 (1.01-1.18)	0.03
Duration post-extubation non-invasive ventilation[c]	1.8 (0.7-6.5) (n=911)	2.0 (0.7-6.3) (n=613)	0.12(0.10-0.16)	0.67	0.95 (0.75-1.19)	0.67
Pediatric ICU length of stay	5.0 (3.0-9.0) (n=5646)	5.0 (3.0-9.0) (n=4849)	0.00(0.00-0.00)	0.83	0.99 (0.92-1.07)	0.83
Hospital length of stay	8.4 (4.5-17.9) (n=4922)	8.4 (4.9-17.6) (n=4236)	0.59(0.41-0.79)	0.02	0.91 (0.84-0.99)	0.02
	N(%)		% Point Difference (95% CI)		Relative Risk (95% CI)[d]	
Successful extubation [e]	5092 (98.6) (n=5163)	4466 (98.6) (n=4530)	0.87(-0.14-1.89)	0.09	1.01 (1.00-1.02)	0.07
Unplanned extubation	167 (3.0) (n=5646)	123 (2.5) (n=4849)	0.85(-0.36-2.07)	0.17	1.58 (1.05-2.37)	0.03
Reintubation[f]	600 (10.6) (n=5646)	551 (11.4) (n=4849)	-0.11(-3.16-2.94)	0.95	1.09 (0.89-1.33)	0.42
Post-extubation non-invasive ventilation	916 (17.5) (n=5226)	616 (13.5) (n=4570)	8.19(3.53-12.84)	0.001	1.22 (1.01-1.49)	0.04
Tracheostomy [g,h]	48 (0.9) (n=5646)	34 (0.7) (n=4849)	0.17(-0.21-0.54)	0.38	0.84 (0.34-2.07)	0.71
Post-extubation stridor[i]	512 (9.1) (n=5646)	423 (8.7) (n=4849)	2.88(-2.21-7.97)	0.27	0.91 (0.72-1.16)	0.45
Pediatric ICU mortality	230 (4.1) (n=5639)	186 (3.8) (n=4848)	0.00(-2.16-2.16)	1.00	1.01 (0.70-1.46)	0.94
Hospital mortality[j]	282 (5.4) (n=5204)	213 (4.8) (n=4454)	0.44(-2.38-3.25)	0.76	1.13 (0.80-1.58)	0.49

Footnotes:

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

b 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 mortalityf The binomial regression model with a small sample correction failed to converge, therefore the Poisson regression with robust standard errors (to correct for misspecification of Poisson distribution for binomial distribution) was used to estimate the Relative Risk.
g Laryngeal edema, resulting in stridor upon extubation; h Includes ICU mortality

eTable 9. Intra-cluster Correlation Coefficient variance components

Main Clinical Outcomes	Intra-cluster correlation coefficient (95% CI)
Prolonged ventilation cohort	
Successful extubation	0.001 (0.0001-0.013)
Unplanned extubation	0.003 (0.001-0.008)
Reintubation	0.017 (0.008-0.038)
Incidence post-extubation NIV	0.050 (0.026-0.096)
Tracheostomy insertion	0.004 (0.001-0.012)
Post-extubation stridor	0.042 (0.021-0.082)
PICU mortality	0.007 (0.003-0.016)
Hospital mortality	0.009 (0.004-0.020)
All children	
Successful extubation	0.001 (0.0002-0.007)
Unplanned extubation	0.002 (0.001-0.007)
Reintubation	0.011 (0.005-0.026)
Incidence post-extubation NIV	0.040 (0.021-0.078)
Tracheostomy insertion	0.004 (0.001-0.011)
Post-extubation stridor	0.045 (0.023-0.085)
PICU mortality	0.007 (0.003-0.015)
Hospital mortality	0.009 (0.004-0.020)

The ICC describes how strongly observations within a cluster resemble each other. The ICC index ranges from 0 (the observations within clusters are no more similar than observations from different clusters) to 1 (all observations in a cluster are identical). To estimate the intra-cluster correlations, a linear mixed effects regression model with an identity-link was fitted, with a random cluster effect and fixed period effect and fixed intervention effect.

eTable 10. Adverse and serious adverse events (prolonged ventilation cohort)

	Events	Number of Events			Number of Patients		
		Total N	Intervention n (%)	Usual Care n (%)	Total N (%)	Intervention n (%)	Usual Care n (%)
SAEs	**Total**	43	18 (41.9)	25 (58.1)	41 (0.5)	18 (0.4)	22 (0.6)
	Related[a]	3	3 (100)	0 (0)	3 (0.03)	3 (0.1)	0 (0)
	Category						
	Cardiovascular	5	3 (60.0)	2 (40.0)	5 (0.1)	3 (0.1)	2 (0.1)
	Dislodgement (non-vascular)	9	2 (22.2)	7 (77.8)	7 (0.1)	2 (0.04)	5 (0.1)
	Dislodgement (vascular)	3	1 (33.3)	2 (66.7)	3 (0.03)	1 (0.02)	2 (0.1)
	Other	1	1 (100)	0 (0)	1 (0.01)	1 (0.02)	0 (0)
	Respiratory[b]	20	9 (45.0)	11 (55.0)	20 (0.2)	9 (0.2)	11 (0.3)
	Thromboembolic	5	2 (40.0)	3 (60.0)	5 (0.1)	2 (0.04)	3 (0.1)
AEs	**Total**	279	113 (40.5)	166 (59.5)	224 (2.5)	88 (1.9)	136 (3.3)
	Related	17	15 (88.2)	2 (11.8)	15 (0.2)	13 (0.3)	2 (0.1)
	Allergy	2	0 (0)	2 (100)	2 (0.02)	0 (0)	2 (0.1)
	Cardiovascular	12	4 (33.3)	8 (66.7)	12 (0.1)	4 (0.1)	8 (0.2)
	Dislodgement (non-vascular)	68	29 (42.7)	39 (57.4)	52 (0.6)	23 (0.5)	29 (0.7)
	Dislodgement (vascular)	100	53 (53.0)	47 (47.0)	89 (1.0)	43 (0.9)	46 (1.1)
	Infection	6	0 (0)	6 (100)	6 (0.1)	0 (0)	6 (0.1)
	Metabolic	3	0 (0)	3 (100)	3 (0.03)	0 (0)	3 (0.1)
	Neurological	6	0 (0)	6 (100)	6 (0.1)	0 (0)	6 (0.1)
	Other	3	1 (33.3)	2 (66.7)	3 (0.03)	1 (0.02)	2 (0.1)
	Respiratory[b]	68	20 (29.4)	48 (70.6)	61 (0.7)	20 (0.4)	41 (1.0)
	Skin/Mucus Membranes	7	5 (71.4)	2 (28.6)	7 (0.1)	5 (0.1)	2 (0.1)
	Thromboembolic	5	2 (40.0)	3 (60.0)	5 (0.1)	2 (0.04)	3 (0.1)

AE, adverse event; SAE, Serious Adverse Event; (a) Where an event is assessed as possibly, probably or definitely related, the event is considered ‘related’ to the SANDWICH intervention. These events were possibly related and were expected events as listed in the study protocol; (b) the most common respiratory reason was hypoxia

eTable 11. Adverse and serious adverse events (all children)

	Events	Number of Events			Number of Patients		
		Total N	Intervention n (%)	Usual Care n (%)	Total N (%)	Intervention n (%)	Usual Care n (%)
SAEs	**Total**	47	21 (44.7)	26 (55.3)	44 (0.4)	20 (0.3)	24 (0.5)
	Related[a]	3	3 (100)	0 (0)	3 (0.03)	3 (0.1)	0 (0)
	Category						
	Cardiovascular	5	3 (60.0)	2 (40.0)	5 (0.05)	3 (0.1)	2 (0.04)
	Dislodgement (non-vascular)	11	4 (36.4)	7 (63.6)	8 (0.1)	3 (0.1)	5 (0.1)
	Dislodgement (vascular)	4	1 (25.0)	3 (75.0)	4 (0.04)	1 (0.02)	3 (0.1)
	Other	1	1 (100)	0 (0)	1 (0.01)	1 (0.02)	0 (0)
	Respiratory[b]	21	10 (47.6)	11 (52.4)	21 (0.2)	10 (0.2)	11 (0.2)
	Thromboembolic	5	2 (40.0)	3 (60.0)	5 (0.1)	2 (0.04)	3 (0.1)
AEs	**Total**	305	128 (42.0)	177 (58.0)	242 (2.3)	96 (1.7)	146 (3.0)
	Related	18	16 (88.9)	2 (11.1)	16 (0.1)	14 (0.3)	2 (0.04)
	Related and unexpected	1	1 (100)	0 (0)	1 (0.01)	1 (0.02)	0 (0)
	Allergy	2	0 (0)	2 (100)	2 (0.02)	0 (0)	2 (0.04)
	Cardiovascular	12	4 (33.3)	8 (66.7)	12 (0.1)	4 (0.1)	8 (0.2)
	Dislodgement (non-vascular)	75	34 (45.3)	41 (54.7)	57 (0.5)	26 (0.5)	31 (0.6)
	Dislodgement (vascular)	114	62 (54.4)	52 (45.6)	99 (0.9)	48 (0.9)	51 (1.0)
	Infection	6	0 (0)	6 (100)	6 (0.1)	0 (0)	6 (0.1)
	Metabolic	5	0 (0)	5 (100)	5 (0.05)	0 (0)	5 (0.1)
	Neurological	6	0 (0)	6 (100)	6 (0.1)	0 (0)	6 (0.1)
	Other	3	1 (33.3)	2 (66.7)	3 (0.03)	1 (0.02)	2 (0.04)
	Respiratory[b]	71	21 (29.6)	50 (70.4)	64 (0.6)	21 (0.4)	43 (0.9)
	Skin/Mucus Membranes	8	6 (75.0)	2 (25.0)	8 (0.1)	6 (0.1)	2 (0.04)
	Thromboembolic	5	2 (40.0)	3 (60.0)	5 (0.1)	2 (0.04)	3 (0.1)

AE, adverse event; SAE, Serious Adverse Event; (a) Where an event is assessed as possibly, probably or definitely related, the event is considered 'related' to the SANDWICH intervention. These events were possibly related and were expected events as listed in the study protocol; (b) the most common respiratory reason was hypoxia

eTable 12. Baseline ventilation parameters

Ventilation Parameter Mean (SD)	Intervention	Usual Care
Ventilator Rate		
Prolonged IMV cohort	26.5 (8.6) n=3425	25.5 (8.2) n=3265
All Children	26.0 (8.6) n=3882	25.1 (8.2) n=3637
FiO_2		
Prolonged IMV cohort	0.37 (0.2) n=4028	0.4 (0.2) n=3525
All Children	0.36 (0.2) n=4591	0.4 (0.2) n=3932
PIP		
Prolonged IMV cohort	19.1 (4.8) n=3719	19.1 (4.7) n=3290
All Children	18.8 (4.8) n=4250	18.9 (4.6) n=3680
PEEP		
Prolonged IMV cohort	5.9 (1.4) n=3858	6.0 (1.5) n=3435
All Patients	5.8 (1.4) n=4414	6.0 (1.5) n=3840
Tidal Volume		
Prolonged IMV cohort	95.0 (106.3) n=880	96.4 (107.7) n=1056
All Children	98.6 (108.1) n=984	99.0 (108.5) n=1160
Level of Pressure Support above PEEP		
Prolonged IMV cohort	11.22 (4.1) n=3478	11.6 (3.4) n=2780
All Children	11.06 (4.1) n=3983	11.5 (3.3) n=3086

FiO2, fraction of inspired oxygen; IMV, invasive mechanical ventilation; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure

eTable 13. Comparison of ventilation parameters two hours prior to extubation (control period) and prior to the start of SBT (intervention period)

Ventilation Parameter Prior to extubation Mean (SD)	Intervention	Usual Care	Mean Difference (95% CI)
Ventilator Rate			
Prolonged IMV cohort	16.4 (7.7) n=1897	16.8 (7.9) n=2500	0.29 (-0.54, 1.11) p=0.50
All Children	16.5 (7.5) n=2250	16.9 (7.8) n=2981	0.29 (-0.47, 1.04) p=0.46
FiO_2			
Prolonged IMV cohort	0.3 (0.1) n=2747	0.3 (0.1) n=4315	-0.01 (-0.02, -0.003) p=0.01
All Children	0.3 (0.1) n=3230	0.3 (0.1) n=5042	-0.01 (-0.02, -0.01) p=0.001
PIP			
Prolonged IMV cohort	14.8 (3.2) n=2528	14.7 (3.7) n=3485	0.05 (-0.28, 0.38) p=0.76
All Children	14.8 (3.2) n=2974	14.7 (3.7) n=4120	0.03 (-0.28, 0.33) p=0.86
PEEP			
Prolonged IMV cohort	5.4 (1.0) n=2715	5.5 (1.0) n=4256	-0.11 (-0.20, -0.02) p=0.01
All Children	5.4 (1.0) n=3184	5.5 (1.0) n=4975	-0.07 (-0.15, 0.01) p=0.08
Tidal Volume			
Prolonged IMV cohort	87.9 (104.1) n=333	105.5 (113.9) n=634	7.71 (-21.38, 36.80) p=0.60
All Children	91.1 (105.0) n=380	110.8 (113.9) n=767	2.83 (-24.61, 30.26) p=0.84
Pressure Support above PEEP			
Prolonged IMV cohort	8.0 (2.7) n=2581	8.2 (2.8) n=3383	-0.09 (-0.35, 0.18) p=0.52
All Children	8.1 (2.8) n=3029	8.3 (2.8) n=3916	-0.15 (-0.41, 0.10) p=0.23

FiO2, fraction of inspired oxygen; IMV, invasive mechanical ventilation; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure

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