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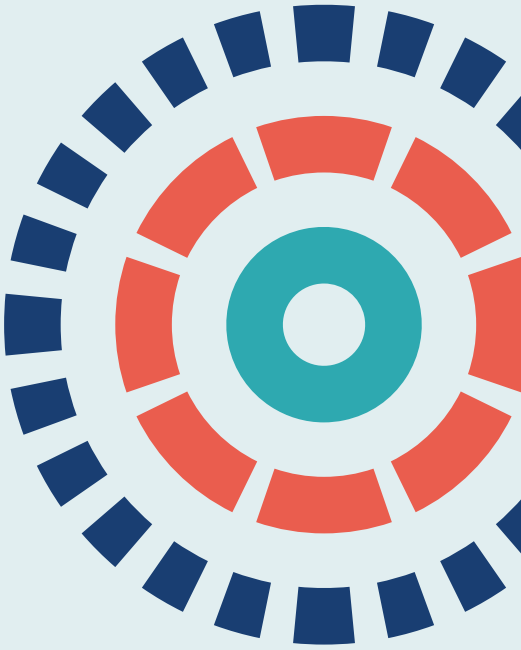

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Protocolised non-invasive compared with invasive weaning from mechanical ventilation for adults in intensive care: the Breathe RCT

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Abstract

Protocolised non-invasive compared with invasive weaning from mechanical ventilation for adults in intensive care: the Breathe RCT

Gavin D Perkins,[1,2]* Dipesh Mistry,[1] Ranjit Lall,[1] Fang Gao-Smith,[2] Catherine Snelson,[3] Nicholas Hart,[4,5] Luigi Camporota,[5] James Varley,[6] Coralie Carle,[7] Elankumaran Paramasivam,[8] Beverly Hoddell,[1] Adam de Paeztron,[1] Sukhdeep Dosanjh,[1] Julia Sampson,[1,2] Laura Blair,[1] Keith Couper,[1,2] Daniel McAuley,[9] J Duncan Young,[10] Tim Walsh,[11] Bronagh Blackwood,[9] Louise Rose,[12] Sarah E Lamb,[1] Melina Dritsaki,[1] Mandy Maredza,[1] Iftekhar Khan,[1,13] Stavros Petrou[1] and Simon Gates[1] on behalf of Breathe collaborators

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Background: Invasive mechanical ventilation (IMV) is a life-saving intervention. Following resolution of the condition that necessitated IMV, a spontaneous breathing trial (SBT) is used to determine patient readiness for IMV discontinuation. In patients who fail one or more SBTs, there is uncertainty as to the optimum management strategy.

Objective: To evaluate the clinical effectiveness and cost-effectiveness of using non-invasive ventilation (NIV) as an intermediate step in the protocolised weaning of patients from IMV.

Design: Pragmatic, open-label, parallel-group randomised controlled trial, with cost-effectiveness analysis.

Setting: A total of 51 critical care units across the UK.

Participants: Adult intensive care patients who had received IMV for at least 48 hours, who were categorised as ready to wean from ventilation, and who failed a SBT.

Interventions: Control group (invasive weaning): patients continued to receive IMV with daily SBTs. A weaning protocol was used to wean pressure support based on the patient's condition. Intervention group (non-invasive weaning): patients were extubated to NIV. A weaning protocol was used to wean inspiratory positive airway pressure, based on the patient's condition.

Main outcome measures: The primary outcome measure was time to liberation from ventilation. Secondary outcome measures included mortality, duration of IMV, proportion of patients receiving antibiotics for a presumed respiratory infection and health-related quality of life.

Results: A total of 364 patients (invasive weaning, $n = 182$; non-invasive weaning, $n = 182$) were randomised. Groups were well matched at baseline. There was no difference between the invasive weaning and non-invasive weaning groups in median time to liberation from ventilation {invasive weaning 108 hours [interquartile range (IQR) 57–351 hours] vs. non-invasive weaning 104.3 hours [IQR 34.5–297 hours]; hazard ratio 1.1, 95% confidence interval [CI] 0.89 to 1.39; $p = 0.352$}. There was also no difference in mortality between groups at any time point. Patients in the non-invasive weaning group had fewer IMV days [invasive weaning 4 days (IQR 2–11 days) vs. non-invasive weaning 1 day (IQR 0–7 days); adjusted mean difference –3.1 days, 95% CI –5.75 to –0.51 days]. In addition, fewer non-invasive weaning patients required antibiotics for a respiratory infection [odds ratio (OR) 0.60, 95% CI 0.41 to 1.00; $p = 0.048$]. A higher proportion of non-invasive weaning patients required reintubation than those in the invasive weaning group (OR 2.00, 95% CI 1.27 to 3.24). The within-trial economic evaluation showed that NIV was associated with a lower net cost and a higher net effect, and was dominant in health economic terms. The probability that NIV was cost-effective was estimated at 0.58 at a cost-effectiveness threshold of £20,000 per quality-adjusted life-year.

Conclusions: A protocolised non-invasive weaning strategy did not reduce time to liberation from ventilation. However, patients who underwent non-invasive weaning had fewer days requiring IMV and required fewer antibiotics for respiratory infections.

Future work: In patients who fail a SBT, which factors predict an adverse outcome (reintubation, tracheostomy, death) if extubated and weaned using NIV?

Trial registration: Current Controlled Trials ISRCTN15635197.

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Glossary

$PaO_2 : FiO_2$ ratio Ratio of arterial oxygen pressure to fraction of inspired oxygen.

List of abbreviations

AE	adverse event
APACHE II	Acute Physiology and Chronic Health Evaluation version II
BHH	Birmingham Heartlands Hospital
BMI	body mass index
CAM-ICU	Confusion Assessment Method-Intensive Care Unit
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CLRN	comprehensive local research network
CONSORT	Consolidated *S*tandards of Reporting Trials
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
CRF	case report form
DHSC	Department of Health and Social Care
DMC	Data Monitoring Committee
EPAP	expiratory positive airway pressure
EQ-5D-3L	EuroQol-5 Dimensions, three-level version
EQ VAS	EuroQol visual analogue scale
FiO_2	fraction of inspired oxygen
GBP	Great British pounds
GCP	good clinical practice
GP	general practitioner
GST	St Thomas' Hospital, London
HDU	high-dependency unit
HR	hazard ratio
HRG	Healthcare Resource Group
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
IMV	invasive mechanical ventilation
INMB	incremental net monetary benefit
IQR	interquartile range
IRR	incidence rate ratio
MAR	missing at random
MI	multiple imputation
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NIV	non-invasive ventilation
OR	odds ratio
$PaCO_2$	partial pressure of carbon dioxide in arterial blood
PaO_2	partial pressure of oxygen in arterial blood
PEEP	positive end-expiratory pressure
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
P_{supp}	pressure support
QALY	quality-adjusted life-year
QEHB	Queen Elizabeth Hospital, Birmingham
RCT	randomised controlled trial
REC	Research Ethics Committee
RR	risk ratio
SAE	serious adverse event
SBT	spontaneous breathing trial
SD	standard deviation
SE	standard error
SF-6D	Short Form questionnaire-6 Dimensions

SF-12	Short Form questionnaire-12 items	VAP	ventilator-associated pneumonia
SpO_2	saturation of oxygen in peripheral blood	VAS	visual analogue scale
TMG	Trial Management Group	WCTU	Warwick Clinical Trials Unit
TSC	Trial Steering Committee		

Plain English summary

Patients who become very unwell may require help from a breathing machine. This requires the patient to be given drugs to put them to sleep (sedation) and have a tube placed through their mouth directly into the windpipe (tube ventilation). This can be life-saving, but may cause harm if used for long periods of time. Non-invasive ventilation (mask ventilation) provides breathing support through a mask that covers the face. Mask ventilation has several advantages over tube ventilation, such as less need for sedation, and it enables the patient to cough and communicate. In previous studies, switching patients from tube to mask ventilation when they start to get better seemed to improve survival rates and reduce complications. The Breathe trial tested if using a protocol to remove tube ventilation and replace it with mask ventilation is better than continuing with tube ventilation until the patient no longer needs breathing machine support.

The trial recruited 364 patients. Half of these patients were randomly selected to have the tube removed and replaced with mask ventilation and half were randomly selected to continue with tube ventilation until they no longer needed breathing machine support. The mask group spent 3 fewer days receiving tube ventilation, although the overall time needing breathing machine help (mask and tube) did not change. Fewer patients in the mask group needed antibiotics for chest infections. After removing the tube, twice as many patients needed the tube again in the mask group as in the tube group. There were no differences between the groups in the number of adverse (harm) events or the number of patients who survived to leave hospital. Mask ventilation was no more expensive than tube ventilation.

In conclusion, mask ventilation may be an effective alternative to continued tube ventilation when patients start to get better in intensive care.

Scientific summary

Background

Invasive mechanical ventilation (IMV) is a life-saving medical intervention. Each year in the UK, 110,000 people require IMV. Acute respiratory failure is the most common indication for IMV. Following resolution of the illness that led to the requirement for IMV, clinical focus shifts to the process of weaning the patient from IMV. A key component of this process is the spontaneous breathing trial (SBT). In a SBT, much of the assistance from the mechanical ventilator is removed, in order to assess the patient's readiness to breathe without its support. Patients who pass the SBT proceed to extubation.

In patients who fail a SBT, the traditional approach has been to continue IMV and to administer a further SBT the following day. However, an alternative approach that has been advocated is to extubate the patient to non-invasive ventilation (NIV). The potential benefits of this approach are the avoidance of further ventilator-induced lung injury, a reduced likelihood of ventilator-associated pneumonia (VAP) and increased patient comfort. The key risk is that, if the strategy fails, the patient will require reintubation, which may be associated with increased mortality.

Sixteen small, typically single-centre, trials ($n = 994$) that compared these approaches were meta-analysed in a Cochrane review (Burns KE, Meade MO, Premji A, Adhikari NK. Noninvasive positive-pressure ventilation as a weaning strategy for intubated adults with respiratory failure. *Cochrane Database Syst Rev* 2013;**12**:CD004127). The review found evidence that the use of NIV in weaning patients from IMV reduced mortality, VAP and duration of mechanical ventilation. However, subgroup analyses found that the beneficial effect was limited to patients with chronic obstructive pulmonary disease (COPD).

In view of the limited generalisability of previous trials to the UK setting and the recognised importance of the clinical issue to the UK critical care community, the National Institute for Health Research (NIHR) Heath Technology Assessment (HTA) programme issued a commissioned call for a study to identify the optimal strategy of liberating patients from IMV.

Objective

The objective of this trial was to determine the clinical effectiveness and cost-effectiveness of NIV as an intermediate step in the protocolised weaning of patients from IMV.

Methods

Design

A pragmatic, open-label, multicentre, randomised controlled trial was conducted to determine if protocolised weaning that includes early extubation on to NIV is clinically effective and cost-effective compared with weaning without NIV (the Breathe trial). The trial was sponsored by Heart of England NHS Foundation Trust. The trial was reviewed and approved by the Oxford C Research Ethics Committee (REC). The trial was managed on a day-to-day basis by a Trial Management Group. Independent oversight was provided through a Trial Steering Committee, and a Data Monitoring and Ethics Committee.

Setting and participants

Patients in critical care units were eligible to participate in the trial if they were aged > 16 years, had received IMV for > 48 hours, were classified as ready to wean by the critical care clinical team and had

failed a SBT. Key exclusion criteria included pregnancy, contraindication to NIV, inability to protect airway because of neurological deficit, and decision not to reintubate or planned withdrawal of treatment.

Interventions

The method [T-piece, continuous positive airway pressure (CPAP) or low-pressure support (P_{supp})] and duration (30–120 minutes) of the SBT were at the discretion of the clinical team. To be deemed to have failed the SBT, the patient were required to meet one of the predefined failure criteria, such as tachypnoea ($\geq$ 50% of baseline value or > 35 breaths per minute), hypercapnia (> 6.5 kPa or increase by > 1 kPa), acidaemia (a pH of < 7.32 or a fall in pH by > 0.07) or increased respiratory effort (e.g. accessory muscle use, facial distress, dyspnoea).

Following confirmation of eligibility and patient consent or consultee agreement, patients were randomised in a 1 : 1 ratio to invasive or non-invasive weaning strategies using an electronic randomisation system. Randomisation was minimised by centre, presence of COPD and reason for critical care admission (postoperative/non-operative).

Participants in the invasive weaning group were returned to P_{supp} ventilation after the failed SBT. P_{supp} was reduced every 2 hours during daytime based on patient condition, in accordance with a weaning protocol. Participants underwent daily SBTs to assess readiness for extubation. The weaning process was followed until a tracheostomy was performed or the participant was extubated.

Participants in the non-invasive weaning group were extubated to NIV after the failed SBT. Initial NIV settings were based on ventilatory settings prior to extubation. P_{supp} was reduced every 2 hours during daytime, based on the participant's condition, in accordance with a weaning protocol. If the participant was considered suitable by the clinical team, a trial of face-mask oxygen was attempted. The weaning process was discontinued when the participant tolerated 12 hours of unsupported spontaneous ventilation.

In both groups, the clinical team titrated fraction of inspired oxygen and/or positive end-expiratory pressure (PEEP)/expiratory positive airway pressure (depending on treatment group) to maintain saturation of oxygen in peripheral blood (SpO_2) of > 90%. The decision to reintubate or perform a tracheostomy was at the discretion of the clinical team, although teams were encouraged not to perform a tracheostomy until at least 7 days after randomisation.

Main outcome measures

The primary effectiveness outcome was time (in hours) from randomisation to successful liberation from ventilation. Liberation from ventilation was defined as the time point at which the patient was free of ventilatory (invasive or non-invasive) support for > 48 hours. Secondary outcomes included mortality (30/90/180 days), duration of IMV, total number of ventilator days (IMV and NIV), time to meeting intensive care unit (ICU) discharge criteria, proportion of patients receiving antimicrobials for presumed respiratory infection and total number of days receiving antimicrobials, reintubation rates and the proportion of patients receiving a tracheostomy. Safety outcomes were adverse events (AEs) and serious adverse events (SAEs). Health-related quality of life (HRQoL) was assessed by the EuroQol-5 Dimensions, three-level version (EQ-5D-3L), and Short Form questionnaire-12 items (SF-12) at baseline (estimated retrospectively), and at 90 and 180 days.

The primary economic outcome was incremental cost per quality-adjusted life-year (QALY) gained from the perspective of the NHS and Personal Social Services.

The original sample size was 920 participants to reliably detect a hazard ratio (HR) of 0.8 between the intervention and control groups for the primary outcome at 80% power, allowing for attrition as a result of ICU death and missing outcome data. This equated to a 36-hour difference in the time to liberation from ventilation, based on an average of 6.4 days in the control group. Interim data analysis identified a skewed data distribution, such that 2.9 days was considered a better estimate for the sample size calculation. Based on these data, it was calculated that a sample size of 280 participants would provide 90% power to

detect a clinically meaningful median difference of 24 hours between the intervention and control groups for the primary outcome at a 5% significance level. This was inflated to 364 participants to account for attrition.

The primary statistical analysis was based on intention-to-treat principles. For analysis of the primary outcome and other time-to-event outcomes, survival analysis methods were used to estimate the HR and the associated 95% confidence interval (CI). For mortality outcomes, logistic regression models were used to estimate the odds ratio (OR) and 95% CIs for differences between groups. Linear regression models were used to estimate the mean treatment difference and 95% CIs for continuous outcomes. For count data, depending on the distribution of the data, negative binomial models were used to estimate the incidence rate ratio and the associated 95% CI or non-parametric tests. All of the analyses were adjusted for age, sex, centre, post-SBT partial pressure of carbon dioxide in arterial blood ($PaCO_2$) and stratification variables (COPD and operative status).

In addition, sensitivity analyses were conducted, namely a per-protocol analysis to explore any apparent baseline differences between the groups. Predefined subgroup analyses comprised presence/absence of COPD and postoperative/non-operative status.

The complementary health economic evaluation examined the cost-effectiveness of interventions. It incorporated the costs of the intervention and the broader health and social care costs over the trial period. Health and social care resource and HRQoL (measured using the EQ-5D-3L and SF-12) data were collected through questionnaires at 3 and 6 months. Multiple imputation was used to impute missing data. For the cost-effectiveness analysis, the incremental cost-effectiveness ratio was estimated as the difference between trial groups in mean total cost divided by the difference in mean total QALYs.

Results

The Breathe trial was conducted between March 2013 and October 2016 across 51 hospitals. In total, 17,126 patients were screened, of whom 1752 underwent a SBT. A total of 432 patients failed the SBT and were therefore eligible for the trial, of whom 68 declined participation and 364 (invasive weaning, $n = 182$; non-invasive weaning, $n = 182$) were randomised.

Groups were well matched at baseline, in relation to demographics, diagnosis, ventilation/haemodynamic characteristics and the SBT process. The mean age of participants was 63.1 years [standard deviation (SD) 14.8 years] and half were male ($n = 184$, 50.5%). The mean duration of ventilation prior to randomisation was 5.8 days (SD 3.5 days). The two most common diagnoses were pneumonia/respiratory infection ($n = 130$, 35.7%) and post-surgery respiratory failure ($n = 78$, 21.4%). The mean baseline PEEP was 6.2 cmH_2O (SD 1.8 cmH_2O) and $PaCO_2$ was 5.7 kPa (SD 1.3 kPa). The most common SBT strategy was CPAP with a mean duration of 47.4 minutes (SD 36.5 minutes). Tachypnoea and increased respiratory effort were the most frequently cited reasons for SBT failure.

Treatment compliance was high in both groups (invasive weaning $n = 158$, 86.8%; non-invasive weaning $n = 175$, 96.2%). Follow-up data at 3 and 6 months were available for 186 (51%) participants in the invasive weaning group and 177 (49%) participants in the non-invasive weaning group.

For the primary outcome, the median time to liberation from ventilation was similar between groups {invasive weaning 108 hours [interquartile range (IQR) 57–351 hours vs. non-invasive weaning 104.3 hours (IQR 34.5– 297 hours); HR 1.10, 95% CI 0.89 to 1.39]. There was also no difference in mortality between groups at any time point [e.g. 30-day mortality in the invasive weaning group was 86.3% ($n = 157$) vs. 86.8% ($n = 158$) for the non-invasive weaning group; adjusted OR 0.90, 95% CI 0.51 to 1.73].

There was no difference in median total (non-invasive and invasive) ventilator days between groups [invasive weaning 4 days (IQR 2–12 days) vs. non-invasive weaning 3 days (IQR 1–9 days); adjusted mean

difference –2 days, 95% CI –4.61 to 0.69]. However, participants in the non-invasive weaning group had fewer IMV days [invasive weaning 4 days (IQR 2–11 days) vs. non-invasive weaning 1 day (IQR 0–7 days); adjusted mean difference –3.1 days, 95% CI –5.75 to –0.51]. In addition, fewer participants in the non-invasive weaning group required antibiotics for a respiratory infection than participants in the invasive weaning group (OR 0.60, 95% CI 0.41 to 1.00).

A higher proportion of participants in the non-invasive weaning group required reintubation than those in the invasive weaning group (OR 2.00, 95% CI 1.27 to 3.24). The frequencies and types of AEs and SAEs were similar between groups. Findings from subgroup and sensitivity analyses were similar to those from the main analysis.

In the cost-effectiveness analysis, a complete QALY profile was available for 182 (50%) participants. Between randomisation and hospital discharge, mean cost was similar between groups [invasive weaning £32,052 vs. non-invasive weaning £29,697; mean difference –£2355, 95% CI –£7292 to £2750]. HRQoL outcomes were similar between groups. The within-trial economic evaluation showed that NIV was associated with a lower net cost and a higher net effect and was dominant in health economic terms; the probability that NIV was cost-effective was estimated at 0.58 at a cost-effectiveness threshold of £20,000 per QALY.

Conclusions

Protocolised weaning that included early extubation to NIV did not reduce overall time to liberation from ventilation. However, patients who underwent non-invasive weaning were less likely to require respiratory antibiotics and had fewer days requiring IMV. The economic evaluation revealed that the non-invasive weaning has some potential to be cost-effective.

In patients who fail a SBT, which factors predict an adverse outcome (reintubation, tracheostomy, death) if extubated and weaned using NIV?

Trial registration

This trial is registered as ISRCTN15635197.

Funding

Funding for this study was provided by the HTA programme of the NIHR.

Chapter 1 Introduction

Scientific background

The widespread use of positive-pressure ventilation in intensive care units (ICUs) can be traced back to the polio epidemic in Denmark in 1952. Among a cohort of 316 patients admitted to hospital with polio affecting the bulbar muscles, mortality fell from 80% to 23% following the introduction of early tracheostomy and positive-pressure ventilation.[1] The lack of mechanical ventilators at the time required teams of medical students to work around the clock in shifts to provide positive-pressure ventilation manually. The demonstrated life-saving potential of invasive positive-pressure ventilation led to an acceleration in the development of mechanical ventilators and the birth of modern-day intensive care.[2]

Epidemiology of positive-pressure ventilation

Each year, an estimated 20 million people worldwide receive invasive mechanical ventilation (IMV).[3] In the UK, approximately 110,000 people require IMV annually.[4] In a large cohort study, the main reasons for requiring mechanical ventilation were acute respiratory failure (69%), coma (16%), acute exacerbation of chronic lung disease (10%) and neuromuscular disease (2%). The causes of acute respiratory failure were postoperative (20%), pneumonia (14%), congestive cardiac failure (10%), sepsis (9%), trauma (8%), acute respiratory distress syndrome (4.5%) and other (12%).[5,6] Reports from the Intensive Care National Audit and Research Centre (ICNARC) indicate that the median duration of ventilation is 5 days [interquartile range (IQR) 3–10 days] and the median length of stay on an ICU is 7 days (IQR 4–14 days).[4] Patients spend, on average, 17 days in hospital (IQR 9–31 days). Mortality during ICU admission has fallen over recent years and is currently around 28%.[5,6]

Weaning from ventilation

Weaning is the process of liberating a patient from mechanical ventilation. It involves transferring the work of breathing from the ventilator to the patient. Weaning accounts for 40–50% of the time a patient requires positive-pressure ventilation.[7] Strategies to optimise weaning should find a balance between withdrawing ventilator support too early and unnecessarily prolonging ventilation. Premature withdrawal runs the risk of reintubation, which is associated with prolonged hospital stay, increased costs, increased tracheostomy use and increased mortality.[8,9] By contrast, delayed weaning is associated with increased adverse effects, such as ventilator-associated pneumonia (VAP),[10,11] sinusitis,[12] upper airway damage,[13] respiratory muscle weakness[13] and increased mortality.[14,15] The requirement for sedative and muscle relaxant drugs during mechanical ventilation may further contribute to delirium, immobility and generalised weakness.[16] The observations that 10–15%[7] of patients require reintubation during the weaning process and that almost half of patients with an unplanned self-extubation during the weaning period do not require reintubation[17] suggest that there is scope for improvement in current weaning approaches.

Weaning involves several stages (*Figure 1*). After treating the underlying illness and ensuring that there are no contraindications to weaning, a spontaneous breathing trial (SBT) is undertaken.[7] During a SBT, minimal support is provided from the ventilator and a combination of clinical and physiological measurements is used to determine whether or not the patient can breathe unaided.

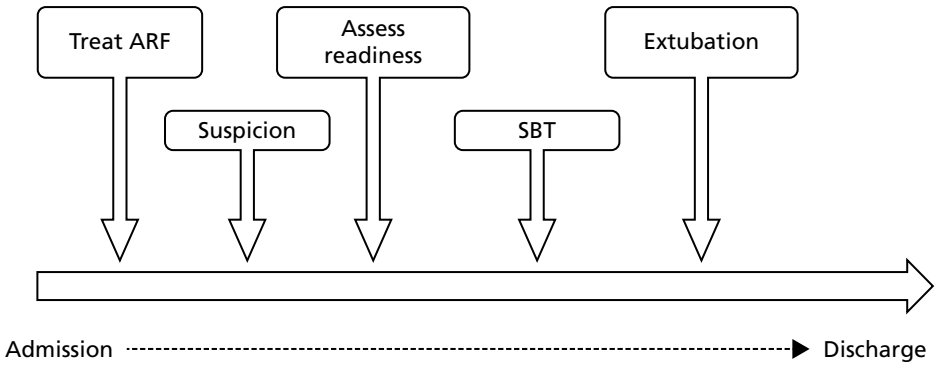


FIGURE 1 Steps involved in liberating a patient from IMV. ARF, acute respiratory failure.

Patients who 'pass' the SBT and are considered otherwise ready for extubation have their tube removed. This group of patients, which represents two-thirds of mechanically ventilated patients, has a good prognosis, with an ICU mortality of approximately 5%.[7] The one-third of patients who 'fail' the SBT have a reported mortality of 25–30%.[7] Weaning practices after failing an initial SBT are variable. SBTs are often repeated on a daily basis until either extubation or a tracheostomy is performed.

Non-invasive ventilation as an adjunct to weaning

Non-invasive ventilation (NIV) refers to the delivery of mechanical ventilation using a mask, nasal pillows, helmet or mouthpiece interface instead of an endotracheal tube. Similar to IMV, NIV reduces the work of breathing and can improve gas exchange.[18] NIV may avoid some complications associated with prolonged endotracheal intubation, such as VAP, sinusitis and ventilator-induced lung injury.[19] In the context of weaning, NIV has been used to facilitate early extubation, to prevent respiratory failure after extubation in high-risk patients and as a rescue therapy when respiratory failure occurs following extubation.[18]

Existing knowledge

A Cochrane review examined the effectiveness of NIV for weaning from IMV across 16 randomised controlled trials (RCTs) that recruited 994 patients.[20] Nine trials enrolled only patients with chronic obstructive pulmonary disease (COPD), whereas seven trials included mixed or non-COPD populations. The review found strong evidence that weaning using NIV reduced mortality [risk ratio (RR) 0.53, 95% confidence interval (CI) 0.36 to 0.80], although heterogeneity was moderate ($I^2 = 37\%$). The beneficial effect seemed limited to studies that enrolled only patients with COPD (RR 0.36, 95% CI 0.24 to 0.56) in contrast to the studies that enrolled mixed populations (RR 0.81, 95% CI 0.47 to 1.40). As shown in *Table 1*, NIV in this context had a number of other benefits.

Need for a trial

The generalisability of the findings from the Cochrane review[20] to current UK practice is limited. There are four main reasons for this. First, the treatment pathway for an exacerbation of COPD has changed since these early trials were conducted. Many patients who would have previously received IMV for respiratory failure now have ward- or ICU-based NIV as a strategy to prevent the need for IMV.[21] IMV is now reserved mainly for patients who fail a trial of NIV. The population of patients ventilated for COPD in contemporary UK practice therefore differs from that enrolled in trials ≥ 10 years ago. Second, none of the trials recruited patients from the UK. This research team's collaboration in the International Survey of Weaning practices

TABLE 1 Effect of non-invasive weaning on clinically relevant outcomes

Outcome	Patient population	
	COPD	Mixed
Weaning failure, RR (95% CI)	0.52 (0.36 to 0.74)	0.73 (0.35 to 1.51)
Nosocomial pneumonia, RR (95% CI)	0.22 (0.13 to 0.37)	0.38 (0.15 to 0.93)
Hospital LOS (days), mean difference (95% CI)	–6.91 (–10.83 to –1.00)	–4.02 (–9.41 to 1.36)
ICU LOS (days), mean difference (95% CI)	–6.66 (–9.41 to –3.92)	–3.32 (–6.78 to 0.15)
Average total duration of mechanical ventilatory support (days), mean difference (95% CI)	–5.77 (–10.64 to –0.91)	0.17 (–4.01 to 4.35)
Duration of endotracheal mechanical ventilation (days), mean difference (95% CI)	–7.53 (–11.47 to –3.60)	–6.85 (–10.75 to –2.95)
Reintubation, RR (95% CI)	0.49 (0.35 to 0.70)	0.82 (0.47 to 1.43)
Tracheostomy, RR (95% CI)	0.04 (0.00 to 0.60)	0.23 (0.09 to 0.57)
Arrhythmia, RR (95% CI)	2.0 (0.20 to 19.78)	0.74 (0.26 to 2.17)

LOS, length of stay.
Note
Data were extracted from Burns *et al.*[20]

shows marked differences in weaning practices between countries.[22] Third, 3 out of the 12 studies (comprising nearly 20% of patients) are either unpublished or published as abstracts only. This limits assessment of methodological quality, and minimal information is available about the population recruited and the interventions tested. Fourth, when it was possible to assess the methodological quality of index trials, the quality of the methods was variable and eight trials had evidence of being at high risk of bias. There was also variation in the methods used to identify patients for weaning (e.g. four trials used a unique resolution of pulmonary infection criterion, which is rarely used in UK practice) and in the approaches to titration and discontinuation of ventilator support.

Although the results of the Cochrane review[20] are encouraging, the size and limitations of trials conducted to date leave uncertainty as to the clinical effectiveness and cost-effectiveness of NIV as a routine tool to facilitate weaning from mechanical ventilation. This is likely to explain the limited penetration of this weaning approach into UK ICU practice. This topic is important to the intensive care community. The need for additional trials in this area was identified by the Intensive Care Society during its Research Prioritisation Exercise in 2008.[23] With these considerations it was timely to conduct a well-designed, appropriately powered randomised control trial (RCT) to examine the clinical effectiveness and cost-effectiveness of NIV-facilitated weaning in the NHS.

The UK's National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme called for applications to examine the clinical effectiveness and cost-effectiveness of using NIV as an intermediate step in weaning patients from IMV.

The objective of the trial was defined in the commissioning brief (*Table 2*).

The Breathe trial investigators were competitively selected to conduct a pragmatic, randomised, controlled, open, multicentre, effectiveness trial to determine if the use of NIV as an intermediate step in the protocolised weaning of patients from IMV is clinically effective and cost-effective.

TABLE 2 The NIHR HTA programme 10/134 commissioning brief

Research question	What is the clinical effectiveness and cost-effectiveness of using NIV as an intermediate step in weaning patients off IMV?
Technology	NIV as an intermediate step in the protocolised weaning of patients off IMV
Patient group	Patients with respiratory failure requiring IMV
Setting	ICUs
Control/comparator treatment	Protocolised weaning that does not include the use of NIV
Design	RCT with internal pilot study. The pilot study should include clear continuation criteria, including an assessment of the likelihood of satisfactory recruitment to the full trial
Important outcomes	Reintubation rate, time from extubation to meeting discharge criteria, ventilator days, cost-effectiveness. Other outcomes: adverse events, ICU LOS, mortality
Minimum follow-up	1 month

LOS, length of stay.

Chapter 2 Methods and assessment

Trial summary

The Breathe trial was a pragmatic, randomised, controlled, open-label, multicentre, effectiveness trial to determine if protocolised weaning that includes early extubation on to NIV is clinically effective and cost-effective compared with weaning without NIV.

Patients with respiratory failure who had received IMV for > 48 hours (from the time of intubation) and failed a SBT were randomised in a 1 : 1 ratio to either the invasive or the non-invasive weaning strategy.

Data were collected on patient demographic characteristics, mechanical ventilation and other relevant variables relating to acute care. Variables required to determine health-related quality of life (HRQoL) were sought from all surviving patients at 90 and 180 days after randomisation.

The primary effectiveness outcome was time from randomisation to successful liberation from ventilation. Liberation from ventilation was defined as the time point at which the patient was free of ventilatory (invasive or non-invasive) support for > 48 hours.

Secondary clinical outcome measures were mortality at 30, 90 and 180 days; duration of IMV and total ventilator days (IMV and NIV); time to meeting ICU discharge criteria; proportion of patients receiving antimicrobials for presumed respiratory infection and total days receiving antimicrobials; reintubation rates; and the proportion of patients receiving a tracheostomy. Safety outcomes were adverse events (AEs) and serious adverse events (SAEs). HRQoL was assessed by completion of the EuroQol-5 Dimensions, three-level version (EQ-5D-3L), and Short Form questionnaire-12 items (SF-12) at baseline (estimated retrospectively), and at 90 and 180 days.

The primary economic outcome was incremental cost per quality-adjusted life-year (QALY) gained from the perspective of the NHS and Personal Social Services (PSS). Secondary economic outcomes were cost of ICU stay (level 2 or 3 days), cost of hospital stay and utilisation of NHS and PSS resources after discharge.

A within-trial economic evaluation that covered the follow-up period of the RCT (to 180 days after randomisation) and a modelling-based economic evaluation that extrapolated cost-effectiveness over a lifetime time horizon were performed. Both were expressed in terms of incremental cost per QALY gained.

The trial was reviewed and approved by the Oxford C Research Ethics Committee (REC) (REC reference number 12/SC/0515).

Eligibility criteria for participants

Adult patients in a participating ICU who had received IMV continuously for > 48 hours (from the time of intubation) were assessed daily for their readiness to commence weaning. Readiness to wean was assessed and declared by the treating clinician/ICU clinical team. The trial eligibility criteria are presented in *Box 1*.

BOX 1 Eligibility criteria

Patients were eligible to be included in the trial if they met all of the following criteria

- Aged ≥ 16 years.
- Respiratory failure requiring IMV for > 48 hours (from the time of intubation).
- Readiness to wean.
- Failed a SBT.

Patients were ineligible if one or more of the following criteria were met

- Known to be pregnant.
- Presence of tracheostomy.
- Unable to protect airway because of neurological deficit.
- Any absolute contraindication to NIV.
- Home ventilation prior to ICU admission (excluding nocturnal CPAP support).
- Decision not to reintubate or withdrawal of care anticipated.
- Further surgery/procedure requiring sedation planned in next 48 hours.
- Previous participation in the Breathe trial.
- Ventilator unavailable to deliver NIV.

CPAP, continuous positive airway pressure.

Assessment of readiness to start weaning

The clinician with overall responsibility for managing the patient's ICU treatment assessed the patient's readiness to start weaning and to undergo a SBT.

Clinicians were provided with information about the Walsh criteria, which were suggested as guidance to indicate when the patient was ready commence weaning.[24] The Walsh criteria recommend that all the following conditions be met to indicate readiness for weaning:

- co-operative and pain free; good cough
- ratio of partial pressure of oxygen in arterial blood to fraction of inspired oxygen ($PaO_2 : FiO_2$ ratio) of > 24 kPa
- positive end-expiratory pressure (PEEP) of < 10 cmH_2O
- haemoglobin level of > 7 g/dl
- axillary temperature of 36.0–38.5 °C
- vasoactive drugs reduced or unchanged over previous 24 hours
- spontaneous ventilatory frequency of > 6 breaths per minute.

Patients who were judged to be ready to wean were established on pressure support (P_{supp}) ventilation. The level of P_{supp} was titrated to achieve patient comfort, tidal volumes of 6–8 ml per kg of ideal body weight and respiratory rate of < 30 breaths per minute. Once the patient was stable on P_{supp} ventilation for at least 60 minutes, a SBT was undertaken.

Spontaneous breathing trial

A survey of practice identified that there were three main types of SBT used in the UK – a T-piece trial, use of continuous positive airway pressure (CPAP) and low-level P_{supp} (5–7 cmH_2O). A T-piece trial involves the patient breathing spontaneously through their endotracheal tube, with the appropriate inspired oxygen concentration being maintained by a crossflow device (T-piece). CPAP involves leaving a standing pressure of 5–10 cmH_2O, delivered via the ventilator, at the top of the endotracheal tube but with no assistance on inspiration. Low-level P_{supp} provides minimal inspiratory assistance. Clinicians were able to undertake one of these three types of SBT in accordance with local unit practices. The SBT was scheduled to last for at least 30 minutes and could be increased to up to 120 minutes in patients who were considered to be at higher risk of reintubation (e.g. prolonged ventilation, past history of COPD, heart failure).

During the SBT, patients were closely monitored for signs of distress or fatigue as described by the International Consensus Conference on Weaning (*Box 2*).[25] A patient was considered to pass the SBT if no signs of distress or fatigue developed. A patient who displayed any sign of distress or fatigue was judged to have failed the SBT. These patients required further weaning and were potentially eligible to be enrolled in the Breathe trial.

Consent

The two-stage consent process adopted for the Breathe trial maximised patient involvement in the decision-making process. It was developed with support from patient representatives and based on national laws where the trial was being conducted.

First, whenever possible, the patient's view on enrolment was sought. Owing to the presence of an endotracheal tube, which limited communication, and likely recent exposure to sedative drugs, this process consisted of briefly imparting information about the trial and inviting the patient to give a view on participation. If the patient expressed a willingness to be involved or was unwilling to express an opinion, then we proceeded to stage two.

BOX 2 Signs of distress/fatigue as described by the International Consensus Conference on Weaning

Physiological assessment

- Heart rate at ≥ 20% of baseline or > 140 beats per minute.
- Systolic blood pressure ≥ 20% of baseline or > 180 mmHg or < 90 mmHg.
- Cardiac arrhythmias.
- Respiratory rate of ≥ 50% of baseline value or > 35 breaths per minute.
- Respiratory rate (minutes)/tidal volume (l) of > 105 breaths per minute per litre.
    - Arterial blood gases: PaO_2 of < 8 kPa on FiO_2 of ≥ 0.5 or SpO_2 of < 90%.
    - $PaCO_2$ of > 6.5 kPa or an increase of > 1 kPa.
- pH of < 7.32 or a reduction in pH of > 0.07.

Clinical assessment

- Agitation and anxiety.
- Depressed mental status.
- Sweating/clammy.
- Cyanosis.
- Increased respiratory effort (i.e. accessory muscle use, facial distress, dyspnoea).

FiO_2, fraction of inspired oxygen; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; PaO_2, partial pressure of oxygen in arterial blood; SpO_2, saturation of oxygen in peripheral blood.

In stage two, a full overview of the trial was provided to the patient's (personal or professional) consultee. The consultee was asked to express a view on what the patient would have decided if they had capacity to make a decision.

Randomisation

Eligible patients were randomised by a web- or telephone-based secure electronic randomisation system. Randomisation was minimised by centre, presence/absence of COPD and postoperative/non-operative reason for ICU admission to ensure that there was an equal balance between treatment groups. Patients were randomised to invasive or non-invasive weaning groups using a 1 : 1 allocation. The randomisation procedure used variable block sizes to reduce the risk of selection bias. Moreover, all allocations remained concealed prior to randomisation. The study flow diagram is shown in *Figure 2*.

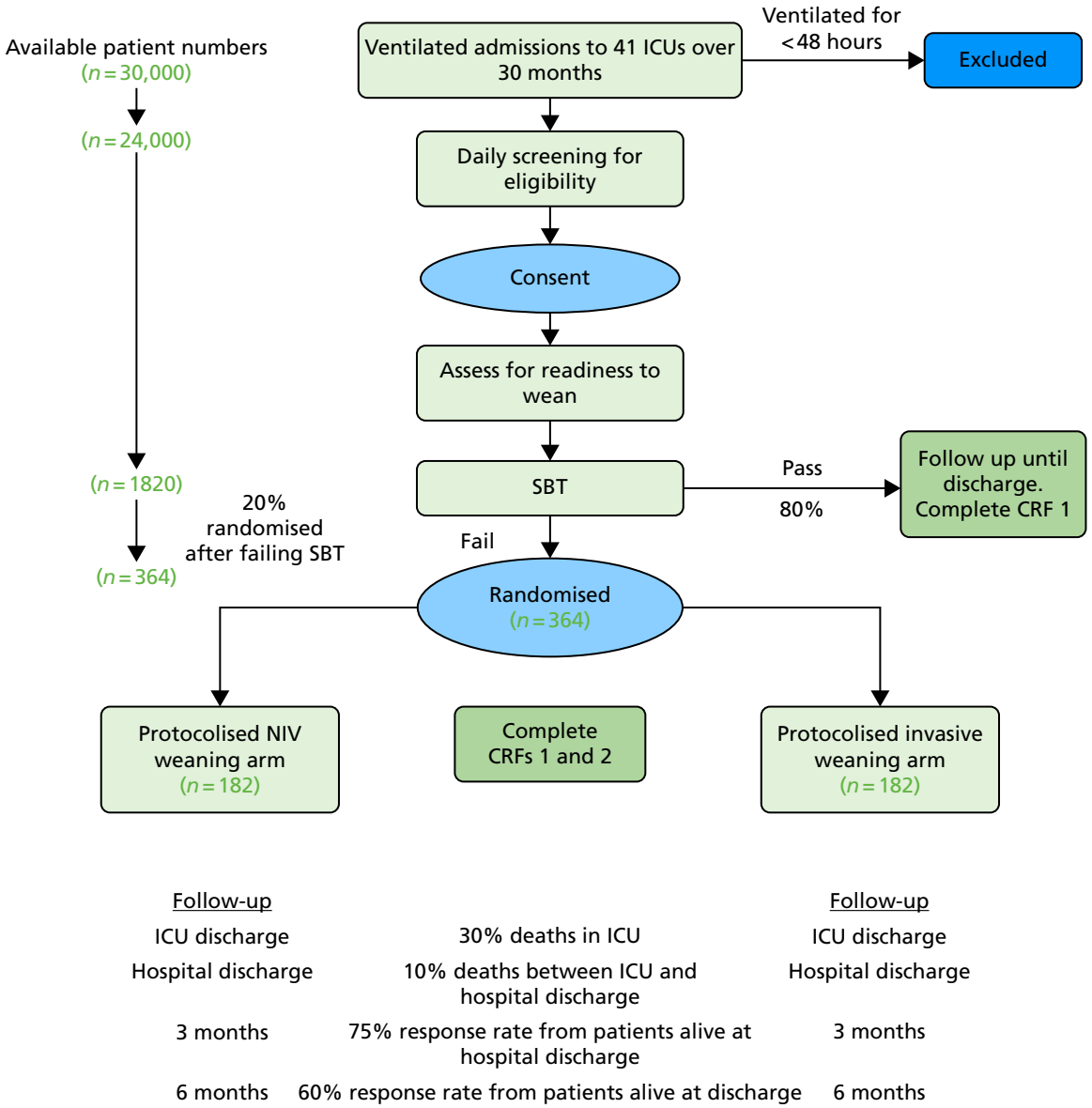


FIGURE 2 Flow diagram. CRF, case report form.

Trial interventions

The health technology being assessed was the use of NIV as an adjunct to protocolised weaning compared with protocolised weaning that does not include NIV, following a failed SBT.

Protocolised invasive weaning group

Participants randomised to the invasive weaning group were re-established on P_{supp} ventilation using the settings that had been in place prior to undertaking the SBT. If necessary, the level of P_{supp} was titrated to achieve patient comfort and a respiratory rate of < 30 breaths per minute. The participant was assessed for signs of distress/fatigue every 2 hours. In the absence of distress/fatigue, P_{supp} was reduced by 2 cmH_2O. This cycle was repeated every 2 hours as tolerated. If, at any point, the participant developed signs of distress/fatigue, then clinical teams sought to identify and treat non-ventilation-associated reversible causes. When these did not lead to a reduction in distress/fatigue, the level of P_{supp} was increased by 2 cmH_2O. The fraction of inspired oxygen (FiO_2) and PEEP were titrated to maintain saturation of oxygen in peripheral blood (SpO_2) of > 90%. This active weaning protocol was used between 08.00 and 22.00. Unless the participant developed signs of distress/fatigue, ventilator settings were not changed overnight. A further SBT was undertaken the next day. This cycle continued until either the participant was extubated (as a result of passing the SBT) or a tracheostomy was performed.

If a participant continued to show signs of distress/fatigue despite increases to P_{supp} and the treatment of any reversible causes, the weaning protocol could be temporarily discontinued and the ventilation strategy determined by the treating clinician. The participant was reassessed at least daily for readiness to wean. When the participant was ready to wean again, the weaning protocol was recommenced. The IMV weaning protocol was discontinued after the participant was extubated.

Non-invasive weaning protocol

Participants randomised to the non-invasive weaning group were re-established on P_{supp} using the settings that had been in place prior to undertaking the SBT. If necessary, the level of P_{supp} was titrated further to achieve patient comfort and a respiratory rate of < 30 breaths per minute. When the participant had recovered from the SBT (physiological parameters had returned to baseline and a clinician judged that they were ready for extubation), they were extubated and immediately provided with NIV with an appropriate level of inspiratory positive airway pressure and expiratory positive airway pressure (EPAP) to match the PEEP and P_{supp} prior to extubation. The level of P_{supp} was titrated to achieve patient comfort and a respiratory rate of < 30 breaths per minute. FiO_2 and EPAP were titrated to maintain SpO_2 of > 90%. The participant was assessed for signs of distress/fatigue every 2 hours. In the absence of distress/fatigue, the treating clinician either removed the NIV to allow a self-ventilation trial or reduced the level of P_{supp} by 2 cmH_2O.

In the self-ventilation trial, supplemental oxygen (equivalent to the previous FiO_2) was provided via a standard oxygen mask and titrated as necessary to maintain SpO_2 of > 90%.

If no signs of distress/fatigue developed during the self-ventilation trial, the trial was continued. If the participant subsequently developed distress/fatigue, NIV was restarted.

If, at any time, the participant developed persistent signs of distress/fatigue/weaning failure, despite increases in P_{supp} and treating any reversible causes, the clinician could temporarily or permanently suspend the weaning protocol.

This active weaning protocol was used between 08.00 and 22.00. Ventilator settings were not changed overnight unless the participant developed signs of fatigue/distress. The NIV weaning protocol was discontinued when the participant tolerated 12 hours of unsupported spontaneous ventilation.

Outcome measures

Primary outcome

The primary outcome measure was time (in hours) from randomisation to liberation from ventilation.

Liberation from ventilation was defined based on the International Consensus Conference on Weaning's recommendations[7] as the time point following which the patient was free of ventilatory (invasive or non-invasive) support for > 48 hours. This defined the duration of weaning process (randomisation to liberation from ventilation).

Reintubation as a consequence of weaning failure generally occurs within the first 12–48 hours.[26] Defining weaning success as being free from ventilator support for 48 hours from liberation of ventilation captured weaning failures (requiring reintubation within 48 hours) but reduced confounding by late events unrelated to the weaning process, such as the need for an unrelated surgical procedure or other event requiring intubation and ventilation.

Secondary outcomes

Secondary outcome measures were:

Efficacy –

- mortality at 30, 90 and 180 days
- duration of IMV and total ventilator days (IMV and NIV)
- time (days) to meeting ICU discharge criteria
- proportion of participants receiving antibiotics for presumed respiratory infection and total of days
- reintubation (met criteria for reintubation and whether or not they were reintubated)
- tracheostomy.

Safety –

- AEs
- SAEs.

Patient-focused outcomes –

- HRQoL: EQ-5D-3L, SF-12 at baseline (estimated), and at 3 and 6 months.

Withdrawal of consent

Participants, their consultee (personal or professional) or the ICU consultant responsible for their care could request withdrawal from the trial at any time without prejudice. In the event that the participant was withdrawn during the protocolised weaning element of the trial, the clinician responsible for their care would determine the safest and most appropriate way to continue the weaning process outside the trial protocol.

In the event of a request to withdraw from the trial, the researcher determined which elements of the trial were to be withdrawn, from the following possibilities:

- the protocolised weaning intervention
- ongoing data collection during hospital admission
- confirmation of status at 30, 90 and 180 days
- contact for follow-up questionnaires.

If the participant requested withdrawal from all four elements, only anonymised data recorded up to the point of withdrawal were included in the trial analysis.

Standardised care protocols and assessments

Daily assessment of need for critical care

Participants were assessed daily (days 0–30) by the clinical team for their need for critical care. Patients are classified as part of national data reporting arrangements in one of four categories.[27] Patients who receive level 0/1 care are classified as requiring ward-based care. Patients who receive level 2/3 care are classified as requiring critical care support.

Level 0: patients whose needs can be met through normal ward care in an acute hospital.

Level 1: patients at risk of their condition deteriorating, or those recently relocated from higher levels of care, whose needs can be met on an acute ward with additional advice and support from the critical care team.

Level 2: patients requiring more detailed observation or intervention, including support for a single failing organ system or postoperative care, and those 'stepping down' from higher levels of care.

Level 3: patients requiring advanced respiratory support alone or basic respiratory support together with support of at least one other organ system. This level includes all complex patients who require support for multiorgan failure.

A participant was considered to have met ICU discharge criteria when they were discharged from the ICU or they no longer required level 2 or level 3 care. This approach was chosen to overcome administrative delays to discharge because of bed capacity issues in the hospital.

Daily assessment of sedation and organ support requirements

The number of sedative drugs administered to the participant in the preceding 24 hours and the number of organs that required support were assessed daily by the clinical team. Organ support requirements were assessed based on the critical care minimum data set definitions of the need for advanced or basic cardiovascular support, advanced or basic respiratory support, and renal support.[28]

Antibiotic use

Whether or not antibiotics had been administered in the previous 24 hours was recorded daily. The clinical team reported whether antibiotics were used primarily for a respiratory or non-respiratory infection. This allowed the calculation of the proportion of participants requiring antibiotics for presumed respiratory infection. In addition, total antibiotic usage (number of days) was calculated.

Criteria for reintubation

The decision to reintubate a participant was a clinical decision, made by the clinician responsible for the participant at the time of assessment. The decision to reintubate or not was complex and included factors outside the predefined reintubation criteria below (e.g. when a subsequent decision to limit treatment was taken).

The following were recorded on a case report form (CRF): when a participant met the predefined reintubation criteria and when they were actually reintubated.

Predefined reintubation criteria were any of the following:

- cardiac or respiratory arrest
- respiratory pauses with loss of consciousness or gasping for air
- severe psychomotor agitation inadequately controlled by sedation
- persistent inability to remove respiratory secretions
- heart rate of ≤ 50 or ≥ 140 beats per minute with loss of alertness
- haemodynamic instability, unresponsive to fluids and vasoactive drugs
- requirement for surgery or other interventional procedure that required deep sedation or anaesthesia.

Criteria for tracheostomy

The decision about the timing of a tracheostomy rested with the treating clinician. It was suggested that a tracheostomy may be considered after at least 7 days after the time of initial intubation. Indications for tracheostomy were (1) persistent requirement for IMV, (2) inability to protect airway and (3) persistent inability to remove respiratory secretions.

Standardised ventilation bundle

The Department of Health and Social Care's (DHSC's) *High Impact Intervention: Care Bundle to Reduce Ventilation-association Pneumonia*[29] mandates ICUs to have sedation protocols and protocols for VAP prevention [head-up position, oral decontamination, sedation hold, peptic ulcer prophylaxis (drug or enteral feeding)] in place. The team ensured that each site had relevant protocols in place.

Blinding

By the nature of the interventions, it was not possible to blind clinicians to whether a participant had been randomised to the invasive or non-invasive treatment group. Careful consideration was given to the strategies that were used to minimise the risk of bias as a consequence of this knowledge.

The use of secure electronic randomisation with a randomisation sequence of variable block size reduced the risk of selection bias. The use of standardised adjunctive care bundles decreased the likelihood of performance bias. The risk of detection bias was minimised by the use of protocols with clear, unambiguous criteria for the discontinuation of IMV and NIV. Intensive care clinical charts provided contemporaneous, hour-by-hour records of a participant's physiology and current treatments. This enabled outcomes to be verified by both site staff and the co-ordinating centre. On the rare occasions that a participant or their legal representative chose to withdraw from the trial, their permission was sought to retain data collected up until that point and to continue to collect the main outcome data. These approaches minimised the risk of attrition bias. Source verification (from clinical records) and hospital computer records were used to minimise the risk of reporting bias. The main clinical and resource utilisation outcomes of this trial [e.g. ventilation status (hourly), death, level 2/3 care, AEs, antibiotic use] were recorded contemporaneously on patient clinical records and hospital information systems.

Schedule of delivery of intervention and data collection

Trial assessments are summarised in *Table 3*. It was anticipated that, after randomisation, most participants would be in the ICU for an average of 5–10 days, followed by a hospital stay of a similar duration. Clinical data were recorded daily during a participant's stay in the ICU. The only daily clinical data that were collected after ICU discharge were antibiotic usage (for antibiotics started in ICU).

Data collection and management

All data for an individual participant were collected by each principal investigator or their delegated nominees and recorded in the CRF. Participant identification in the CRF was through their unique participant trial number, allocated at the time of randomisation, and their initials. Data were collected from the time a participant was considered for entry into the trial through to their discharge from hospital. In the event that a participant was transferred to another hospital, the trial team liaised with the receiving hospital to ensure complete data collection.

Data were collected in duplicate using no-carbon-required forms. Once a participant had been discharged from hospital and all data were entered into the CRF, the top copy of each form was returned to the trial co-ordinating centre. The bottom copy of the CRF was retained at the recruiting centre. The trial number, name, address and other contact details of all participants who survived and agreed to follow-up were supplied

TABLE 3 Trial assessments

Assessment	Visit					
	Initial	ICU stay	Hospital stay	30 days	3 months	6 months
Informed consent	✓					
Medical history	✓					
Inclusion/exclusion criteria	✓					
Intervention	✓	✓				
Clinical variables	✓	✓	✓			
Quality of life/health economic outcomes			✓		✓	✓
AEs		✓	✓	✓		
Survival status		✓	✓	✓	✓	✓

to the trial co-ordinating centre at the time of hospital discharge to allow follow-up questionnaires to be posted to the participant at 3 and 6 months post intervention.

Submitted data were reviewed for completeness and entered onto a secure, backed-up, bespoke database. Due care was taken to ensure data safety and integrity, and compliance with the Data Protection Act 1998.[30]

Data collection used instruments that had been optimised using data collection pilots before recruitment started. Data collection was restricted to those variables required to define patient characteristics at enrolment, to monitor the treatment received, to monitor adverse effects and to determine quality of life and the use of health-care resources.

In brief, the data set included:

- variables describing baseline characteristics –
  - participant identifiers
  - inclusion and exclusion criteria
  - Acute Physiology and Chronic Health Evaluation version II (APACHE II) score (24 hours after admission)
  - admission diagnosis
  - presence of COPD [defined by the British Thoracic Society/National Institute for Health and Care Excellence (NICE) criteria or current treatment for COPD]
  - measured or estimated height and weight, and calculated body mass index
  - duration of ventilation prior to randomisation
  - presence of delirium, as measured by the Confusion Assessment Method-Intensive Care Unit (CAM-ICU).
- variables collected daily from randomisation until discharge from ICU –
  - ventilation status (IMV, NIV, self-ventilating)
  - organ support requirements (defined by the mandatory DHSC Critical Care Minimum Data set)[28]
  - level of ICU support required (level 0–3, for which 0 and 1 define readiness for ICU discharge)
  - antibiotic use for respiratory and non-respiratory infections
  - tracheostomy
  - criteria met for reintubation and actual reintubation
  - AEs
  - deaths
  - sedation use.

- variables collected after ICU discharge –
  - antibiotic use for respiratory and non-respiratory infections started within ICU
  - acute hospital discharge date and status (to calculate acute hospital length of stay).
- variables collected after hospital discharge –
  - vital status up to 180 days post randomisation
  - EQ-5D-3L and SF-12 questionnaire at 3 and 6 months, after verification of vital status with telephone follow-up for non-responders.
  - Health-care resource use questionnaire at 3 and 6 months after verification of vital status with telephone follow-up for non-responders.

Participant survival after discharge from hospital was determined by the trial office contacting a participant's general practice. This information was provided by the participant on the participant contact details form.

All survivors were followed up at 3 and 6 months after randomisation by postal questionnaire. The trial office identified any deaths after discharge from hospital by calling a participant's general practice first to avoid sending questionnaires to participants who had died. Participants were asked to let the co-ordinating centre know if they moved house at any time after hospital discharge. The follow-up questionnaire collected data on disability and HRQoL, using the EQ-5D-3L and SF-12 questionnaires. If questionnaires were not returned, a maximum of two telephone contacts were made to a participant to check that the questionnaire had been received and that the participant was happy to complete it, followed by a second copy of the questionnaire and telephone contacts in the event of non-return. If the second questionnaire was not returned, the participant was contacted and the outcome data were collected over the telephone, when possible.

Estimating baseline health-related quality of life

Owing to the challenges of collecting baseline data from very frail patients, these data were not collected through patient questionnaires. However, assume a baseline utility score of –0.402 (the value assigned by the EQ-5D-3L tariff to an unconscious health state) was assumed and this was considered to be the same for each participant, regardless of underlying heterogeneity in health states.

Database

The database was set up by the Programming Team at Warwick Clinical Trials Unit (WCTU) and all specifications (i.e. database variables, validation checks, screens) were agreed between the programmer, statistician and trial co-ordinator. All data were entered by the data clerk and all data were periodically reviewed by the trial co-ordinator to assure accuracy and consistency. Only authorised and approved members of staff had access to the database.

Data storage

All essential documentation and trial records were stored by WCTU in conformance with the applicable regulatory requirements and access to stored information was restricted to authorised personnel.
All available data can be obtained from the corresponding author.

Archiving

Trial documentation and data will be archived for 5 years after completion of the trial. Trial master files and associated data were archived by WCTU; trial data generated at trial sites were archived in accordance with local policy.

Serious adverse events

A SAE was an AE that fulfilled one or more of the following criteria:

- resulted in death
- was immediately life-threatening
- required hospitalisation or prolongation of existing hospitalisation
- resulted in persistent or significant disability or incapacity
- was a congenital abnormality or birth defect
- any other important medical condition that, although not included in the above, required medical or surgical intervention to prevent one of the outcomes listed.

The causality (i.e. relationship to trial treatment, *Table 4*) and expectedness (expected or unexpected) was assessed by the investigator(s) and recorded on the SAE form.

Related and unexpected SAEs that occurred between trial entry and 30 days post randomisation were reported using the mechanism described in *Chapter 5*, *Measurement of resource use and costs*.

Expected serious adverse events that did not require separate reporting

Because the Breathe trial was recruiting a population that was already in a life-threatening situation, it was expected that many of the participants would experience SAEs. Events that were expected in this population and those that were collected as outcomes of the trial were not reported as SAEs. These included:

- death
- organ failure
- pneumonia
- reintubation
- tracheostomy.

Reporting serious adverse events

All SAEs, as defined above, were entered onto the SAE reporting form and faxed to a dedicated fax at WCTU within 24 hours of the investigator becoming aware of them. Once received, causality and expectedness were confirmed by the chief investigator. SAEs that were deemed to be unexpected and related to the trial were notified to the REC within 15 days. All such events were reported to the sponsor, Trial Steering Committee (TSC) and Data Monitoring Committee (DMC) at their subsequent meetings.

TABLE 4 Relationship of SAEs to trial intervention

Relationship to trial intervention	Description
Unrelated	There was no evidence of any causal relationship
Unlikely to be related	There was little evidence to suggest that there was a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication or device). There was another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment)
Possible relationship	There was some evidence to suggest that there was a causal relationship (e.g. because the event occurred within a reasonable time after administration of the trial medication or device). However, the influence of other factors contributed to the event (e.g. the participant's clinical condition, other concomitant treatments)
Probable relationship	There was evidence to suggest that there was a causal relationship and the influence of other factors was unlikely
Definitely related	There was clear evidence to suggest that there was a causal relationship and other possible contributing factors can be ruled out

All participants who experienced SAEs were followed up as per protocol until the end of the trial.

Adverse events

Participants were screened daily for the following AEs known to be associated with the use of NIV:

- nasal/skin/mouth sores/irritation
- vomiting
- gastric distension
- barotrauma (e.g. pneumothorax)
- non-respiratory infection
- arrhythmia.

Statistical methods

Power and sample size

The original sample size was set at 920 participants to detect a hazard ratio (HR) of 0.8 between the intervention and control groups for the primary outcome with 80% power, allowing for time to discontinuation of ventilation to be undefined for 30% of participants because of death in the ICU, and for 2% of participants to have missing outcome data because of withdrawal from the trial. This equated to 36 fewer hours for the intervention group in the time to liberation from ventilation, based on an average of 6.4 days in the standard care group, drawn from a five-centre audit of weaning duration in the UK.

At the request of the Trial Management Group (TMG), the DMC and TSC reviewed the sample size requirements 18 months into trial recruitment in the light of slower than anticipated recruitment. Analysis of the duration of ventilation among participants in the control group revealed that the distribution of data was skewed, indicating that the median duration of weaning, which was 2.9 days, would be a better estimate for the sample size calculation.

Using a median value of 2.9 days and a minimally clinically important difference of 24 hours provided an associated HR of 1.53. However, it was anticipated that the hazards may not be constant over time (as assumed for the exponential distribution) and that the hazards were quite likely to decrease over time. For this reason, a Weibull distribution was used, as it computes a shape parameter, p, that allows for non-constant hazards. The p-value was estimated to be 0.918, thus giving a HR of 1.48.

Based on these data, a minimum sample size of 280 participants would provide 90% power to detect a clinically meaningful median difference of 24 hours between the intervention and control groups for the primary outcome at a 5% significance level. However, it was anticipated that around 23% of participants would be lost to follow-up. The sample size ($n = 280$) was therefore inflated by 23% to allow for loss to follow-up, resulting in a final sample size of 364 ($n = 182$ participants in each group).

The revised sample size was approved following review by the DMC, TSC and NIHR.

Primary analyses

Data were reported and summarised in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines for RCTs.[31] The primary analysis method for the trial was intention to treat, that is all participants were analysed as part of the group to which they were originally randomised, regardless of what treatment they actually received. Analysis of the primary outcome [time from randomisation to liberation from ventilation (hours)] and other time-to-event outcomes used survival analysis methods to estimate the HR and the associated 95% CI. Logistic regression models were used to estimate the odds ratios (ORs) and 95% CIs for differences in mortality between the two trial groups at 30, 90 and 180 days. Linear regression models were used to estimate the mean treatment difference and 95% CIs for continuous outcomes. The distribution of count data, for example the number of days on advanced

respiratory support, could be either overdispersed with zero inflation, that is several participants with no days on advanced respiratory support, or non-normal. For the former, negative binomial models were used to estimate the incidence rate ratio (IRR) and the associated 95% CI; otherwise, non-parametric tests were applied. All of the analyses were adjusted for age, sex, centre, post-SBT partial pressure of carbon dioxide in arterial blood ($PaCO_2$) and for both of the stratification variables (presence/absence of COPD and whether or not the patient was being treated after surgery).

Sensitivity analyses

A per-protocol analysis was performed as a sensitivity analysis to see how the treatment effect estimate differed when analysed by treatment received. Moreover, additional sensitivity analyses explored the effects of adjustment for any potential baseline differences between the groups.

Subgroup analyses data set access

After data lock, all members of the trial team were able to access the final data set. The chief investigator had full access to the trial data and assumed overall responsibility for the analysis.

Subgroup analyses

In the protocol, it was stated that three predefined subgroup analyses would be undertaken: (1) responsibility for weaning processes (physician led/multiprofessional), (2) presence/absence of COPD and (3) postoperative/non-operative. Of these, data on the first subgroup were not collected; thus, this subgroup analysis was not conducted. Subgroup analyses were performed, for the primary outcome, by the inclusion of interaction terms in the Cox regression models.

Chapter 3 Trial organisation and oversight

Sponsor

The Heart of England NHS Foundation Trust and the University of Warwick acted as cosponsors for the trial. Agreed responsibilities were subcontracted to the University of Warwick, as employer of the chief investigator and co-ordinating centre for the trial.

Subcontracts that delegated responsibilities to research sites were established using the University of Warwick's standard contracting processes with NHS organisations.

Indemnity

NHS indemnity covered NHS staff, medical academic staff with honorary contracts and those conducting the trial. NHS bodies carried this risk themselves or spread it through the Clinical Negligence Scheme for Trusts,[32] which provided unlimited cover for this risk.

The University of Warwick provided indemnity for any harm caused to patients by the design of the research protocol.

Trial timetable and milestones

The trial timetable is displayed in *Table 5*. The first site opened within 3 months of initiating the grant and all sites were open within 12 months. The internal pilot ran between 3 and 9 months from grant initiation. Following successful confirmation of recruitment rates, the internal pilot ran seamlessly into the main trial. Additional trial sites were recruited throughout the recruitment period. As most ICUs have the equipment necessary to deliver NIV, this did not present a challenge.

Criteria for progression to the main trial

The following criteria were used to determine progression from the pilot to the main trial:

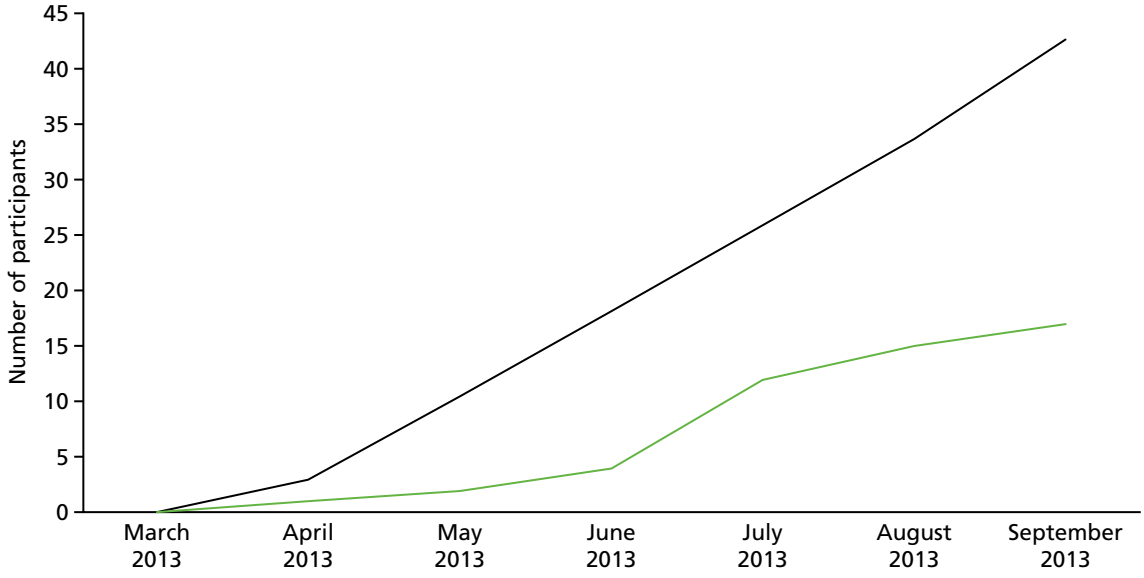
- recruitment > 75% of target (target 32 participants)
- protocol compliance (> 75%)
    - daily sedation hold (yes/no)
    - compliance with allocated intervention (IMV or NIV use)
    - proportion of weaning time within relevant protocol (assessed daily)
    - adherence with ventilator care bundle (yes/no)
- protocol compliance sent to the NIHR HTA programme.

TABLE 5 Trial timetable

	Project activity (months)																
Trial stage	**< 0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	**36**	**39**	**42**	**45**	**48**
Set up																	
Recruit research staff	✓																
Ethics approval	✓																
Refine protocol	✓																
Pilot trial																	
R&D approvals	✓	✓	✓														
Sites open (*n*)		5	7														
Participant recruitment		✓	✓														
3-month follow-up		✓	✓														
6-month follow-up			✓														
Participant accrual (pilot) (*n*)		11	32														
Main trial																	
R&D approvals		✓	✓	✓													
Sites open (*n*)				15	25	25	25	25	25	25	25	25	25				
Participant recruitment				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓				
3-month follow-up				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
6-month follow-up					✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Trial management/reporting																	
Data processing		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Data analysis			✓		✓		✓		✓		✓	✓	✓	✓	✓	✓	
DMC meeting	✓		✓		✓		✓		✓		✓		✓		✓	✓	✓
TSC meeting	✓		✓		✓		✓		✓		✓		✓		✓		
Monitoring reports			✓		✓		✓		✓		✓		✓		✓		
HTA monograph																✓	✓
Other publications	✓ (protocol)													✓	✓	✓	✓
Participant accrual (pilot and main) (*n*)		11	32	77	190	302	415	527	640	752	865	977	1090				

R&D, research and development.

The progression criteria listed above were not met during the pilot phase. Recruitment was < 75% of the target (17/32, 53%; see pilot trial recruitment graph in *Figure 3*) and protocol compliance was also lower than the 75% target. However, the NIHR HTA programme acknowledged that proactive steps to boost recruitment were in place and the trial question remained important. On this basis, it was recommended that the trial progressed from the pilot phase to the main trial.



	March 2013	April 2013	May 2013	June 2013	July 2013	August 2013	September 2013
Target	0	3	11	18	26	34	43
Recruited	0	1	2	4	12	15	17

FIGURE 3 Pilot trial recruitment graph.

Administration

The trial was co-ordinated at WCTU. All day-to-day co-ordination of the trial was the responsibility of the trial co-ordinator. All clinical co-ordination was the responsibility of the chief investigator. The trial was managed by a multidisciplinary team.

The trial office team assisted with and facilitated the setting up of centres that wished to collaborate in the trial. In addition, the trial office team:

- distributed the standardised data collection forms to collaborators
- organised the telephone randomisation service for formal trial entry
- monitored the collection and processing of data, and sought missing data
- trained local staff in recruitment processes and data collection
- ensured the confidentiality and security of all forms and data
- conducted extensive data-checking and cleaning
- organised any interim and main analyses
- organised TMG, TSC, DMC and collaborators' meetings.

The trial office received completed data forms via the postal service. On receipt, data forms were checked for completeness and entered into a trial-specific dedicated computer program that checked the validity of the data.

Patient and public involvement

The Intensive Care Society's Patients and Relatives Committee helped to ensure that the research question, design, conduct and interpretation were considered from the users' perspective. Patient and public involvement in the trial was formally facilitated through the involvement of two representatives on the TSC (a former patient and a relative).

Trial Management Group

The TMG met monthly. Meetings were minuted and a list of actions recorded.

Trial Steering Committee

The role of the TSC was to provide overall supervision for a trial on behalf of the trial sponsor and trial funder and to ensure that the trial was conducted to the rigorous standards set out in the DHSC's Research Governance Framework for Health and Social Care[33] and the Guidelines for Good Clinical Practice (GCP).[34] The TSC membership comprised independent clinicians, methodologists and two patient and public involvement representatives.

The main tasks of the TSC were to:

- provide advice, through its chairperson, to the chief investigator(s), the trial sponsor, the trial funder, the host institution and the contractor on all appropriate aspects of the trial
- monitor the progress of the trial, adherence to the protocol and participant safety, and to consider new information of relevance to the research question
- ensure that the rights, safety and well-being of the trial participants were the most important consideration and that they prevailed over the interests of science and society
- ensure that appropriate ethics and other approvals were obtained in line with the project plan
- agree proposals for substantial protocol amendments and to provide advice to the sponsor and funder regarding approvals of such amendments
- provide advice to the investigators on all aspects of the trial.

The TSC adhered to the following guidelines:

- A minimum of 75% were independent members. Only appointed members were entitled to vote and the chairperson had a casting vote.
- The minimum quoracy for a meeting to conduct business was 67% of appointed members.
- The chairperson and members signed and maintained a log of potential conflicts of interest.
- Attendance at TSC meetings by non-members was at the discretion of the chairperson. The primary TSC reporting line was via the chairperson to the NIHR HTA programme director.

Data Monitoring and Ethics Committee

A DMC was appointed comprising two clinicians with experience in undertaking clinical trials and caring for subjects who are critically ill and a statistician who was independent of the trial.

During the period of recruitment, interim analyses of the proportion of participants alive at 28 days and analyses of deaths from all causes at 28 days were supplied, in strict confidence, to the DMC, along with any other analyses that the committee requested. The intervals for these analyses were determined by the committee.

The DMC advised the chairperson of the TSC if, in their view, the randomised comparisons had provided (1) proof beyond reasonable doubt that for all, or some, the treatment was clearly indicated or clearly contraindicated and (2) evidence that might reasonably be expected to materially influence future patient management.

Following a report from the DMC, the TSC decided what actions, if any, were required. Unless the DMC requested cessation of the trial, the TSC and the collaborators remained blinded to the interim results.

Essential documentation

A trial master file was set up according to WCTU standard operating procedures and was held securely at the co-ordinating centre.

Monitoring and quality assurance of trial procedures

Definitions

Trial protocol deviation

Deviations from clinical trial protocols and GCP occur commonly in clinical studies. The majority of these instances are technical deviations that do not result in harm to the trial subjects or significantly affect the scientific value of the reported results of the trial. These cases were documented in the protocol deviation section of the CRF for the trial and appropriate corrective and preventative actions were taken. Deviations were included and considered when the clinical study report was produced, as they may have had an impact on the analysis of the data. A clinical decision to take the patient 'off protocol' (for the weaning protocol) was recorded in the weaning log as opposed to a trial protocol deviation. Adherence with the weaning regime was recorded in the CRF under the adherence section in the daily data record.

Serious breach

A serious breach was defined as any protocol deviation or breach of the principles of GCP in connection with the Breathe trial that had a significant effect on the safety or physical or mental integrity of the subjects or the scientific value of the trial.

Local monitoring of protocol compliance

The following elements, related to protocol compliance, were assessed daily and recorded on the CRF by a member of the local research team:

- daily sedation hold (yes/no)
- compliance with allocated intervention (IMV or NIV use)
- proportion of weaning time within relevant protocol (assessed daily)
- adherence to ventilator care bundle (yes/no).

Monitoring

All sites were monitored by WCTU during the first few weeks after they were recruited. Monitoring sought to ensure protocol compliance, quality of data collection and storage of documentation. Monitors had access to relevant participant notes/charts and trial documentation. The primary purpose of the monitoring visit was to ensure the safety of the trial participant and the integrity of the trial data. Monitoring visits were conducted in a supportive manner with the objective of supporting centres in delivering the trial safely and in accordance with the principles of GCP.

Participating institutions permitted trial-related monitoring, audits, REC review and regulatory inspections, and provided direct access to source data/documents as required.

Reporting

Protocol deviations (and actions taken to prevent recurrence) were recorded in the CRF. Deviations from the weaning protocol were recorded in the weaning log and daily data form.

Any serious breaches of the trial protocol or GCP were immediately reported to the chief investigator. The chief investigator, in consultation with the principal investigator, took whatever immediate action was required to safeguard the well-being of the participant.

Financial support

Research costs

Research costs for this trial were funded by the NIHR HTA programme (project reference 10/124/06).

NHS service support costs

This trial was included on the NIHR portfolio and received NHS service support costs. NHS service support costs were produced through the lead comprehensive local research network (CLRN) (West Midlands South CLRN). The costing was based on their experience of similar trials in this setting and was calculated as £79.65 per participant.

End of the trial

The trial ended when 364 participants had been randomised and the last participant had completed the final follow-up (28 April 2017).

However, prior to reaching the trial target, it had been agreed that the trial would have been stopped prematurely if:

- mandated by the REC
- following recommendations from the DMC
- funding for the trial ceased.

The REC that originally gave a favourable opinion of the trial would have been notified in writing if the trial had been concluded or terminated early.

Chapter 4 Results

Participant flow

The CONSORT flow diagram in *Figure 4* details the overall flow of participants through the trial.

Recruitment

Recruitment for the overall trial (including the internal pilot trial) occurred between March 2013 and October 2016, when 364 participants were recruited from across 51 hospitals (*Figures 5* and *6*). A total of 17,126 potential participants were identified through the screening process and were assessed for eligibility, of whom 90% (15,374/17,126) were ineligible (see *Figure 4*). A breakdown of the screening process and detailed reasons for exclusion are summarised by site in *Appendix 1*. The remaining 1752 patients underwent a SBT, of whom 75% (1320/1752) passed the SBT and were thus excluded. Of the 432 eligible participants who failed the SBT, 16% (68/432) declined to participate and the remaining 84% (364/432) consented to trial participation and were thus randomised. There were no participants randomised in error. Most patients were randomised between 11.00 and 16.00 (*Figure 7*). The proportion of randomised participants in each group across all sites and also across the randomisation strata is detailed in *Appendix 2*. The three highest-recruiting sites [Birmingham Heartlands Hospital (BHH), Queen Elizabeth Hospital, Birmingham (QEHB) and St Thomas' Hospital, London (GST)] were part of the pilot trial and were therefore open for recruitment for the most time. The screening logs (see *Appendix 1*) from these three sites had higher than average screening rates ($n = 609$, $n = 1838$ and $n = 1054$ for BHH, QEHB and GST, respectively) than the centre average of 335. The proportion of patients excluded after screening was lower than the 90% centre average at BHH (76%) and QEHB (88%). The proportion of patients who underwent a SBT was higher than the centre average of 9% in BHH (24%) in QEHB (12%) and in GST (10%), of whom 34%, 32% and 43%, respectively, of patients failed the SBT (centre average 23%). The proportion of patients who failed the SBT and went on to be randomised was higher than the centre average (81%) at two of these sites: BHH (100%) and GST (100%).

Participant baseline data

Participant baseline and demographic data

The baseline and demographic data of participants are summarised in *Table 6*. Overall, the characteristics of the participants were well matched at baseline between the two treatment groups. Participants had a mean age of around 63 years [standard deviation (SD) 14.8 years]. The proportion of males and females was similar. Around 11% (40/364) had evidence of delirium. The risk of mortality was similar across both groups, with participants having an overall mean APACHE II score of 18.9 (SD 6.4). Most admissions were diagnosed as either pneumonia/respiratory infection (35.7%) or post-surgery respiratory failure (21.4%). The type of diagnosis was similar across both groups, apart from pneumonia/respiratory infection, for which there was around a 9% difference between the two groups (see *Sensitivity analysis*).

Participant baseline physiology data

The baseline physiology data of the trial participants are summarised in *Table 7*. The ventilation measures, haemodynamic measures and arterial blood gas measures were similar across both treatment groups. The distribution of participants' PEEP, P_{supp}, $PaO_2 : FiO_2$ ratio and spontaneous tidal volume is shown in *Figure 8*. Participants required high levels of ventilator support when the mean P_{supp} reported was 11.5 cmH_2O (SD 4.8 cmH_2O). The mean $PaO_2 : FiO_2$ ratio was 33.3 kPa (SD 10.4 kPa).

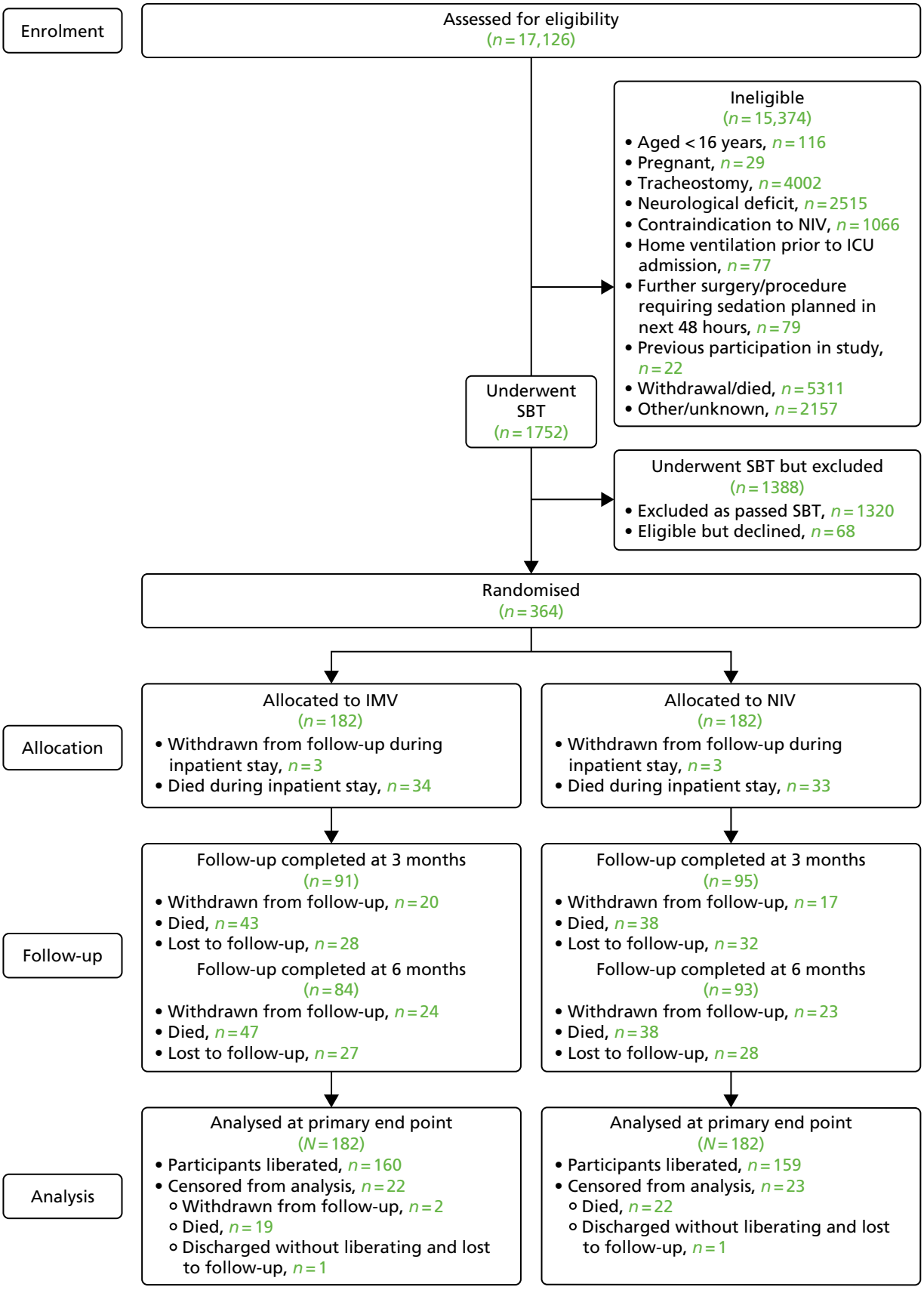


FIGURE 4 The CONSORT flow diagram for the Breathe trial.

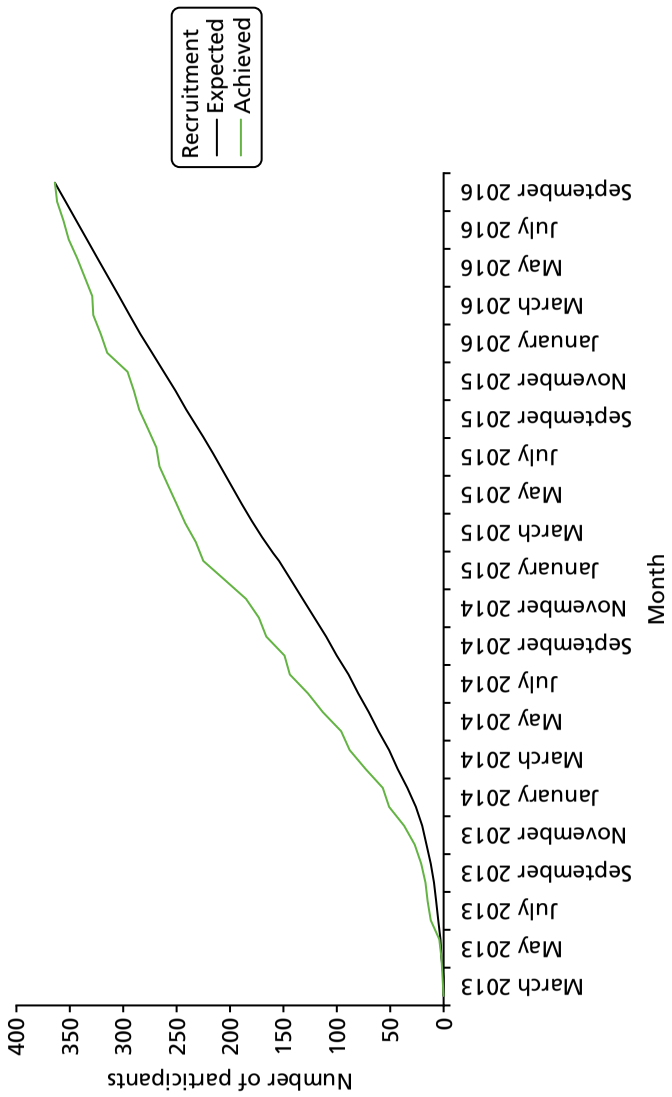


FIGURE 5 Overall trial recruitment graph.

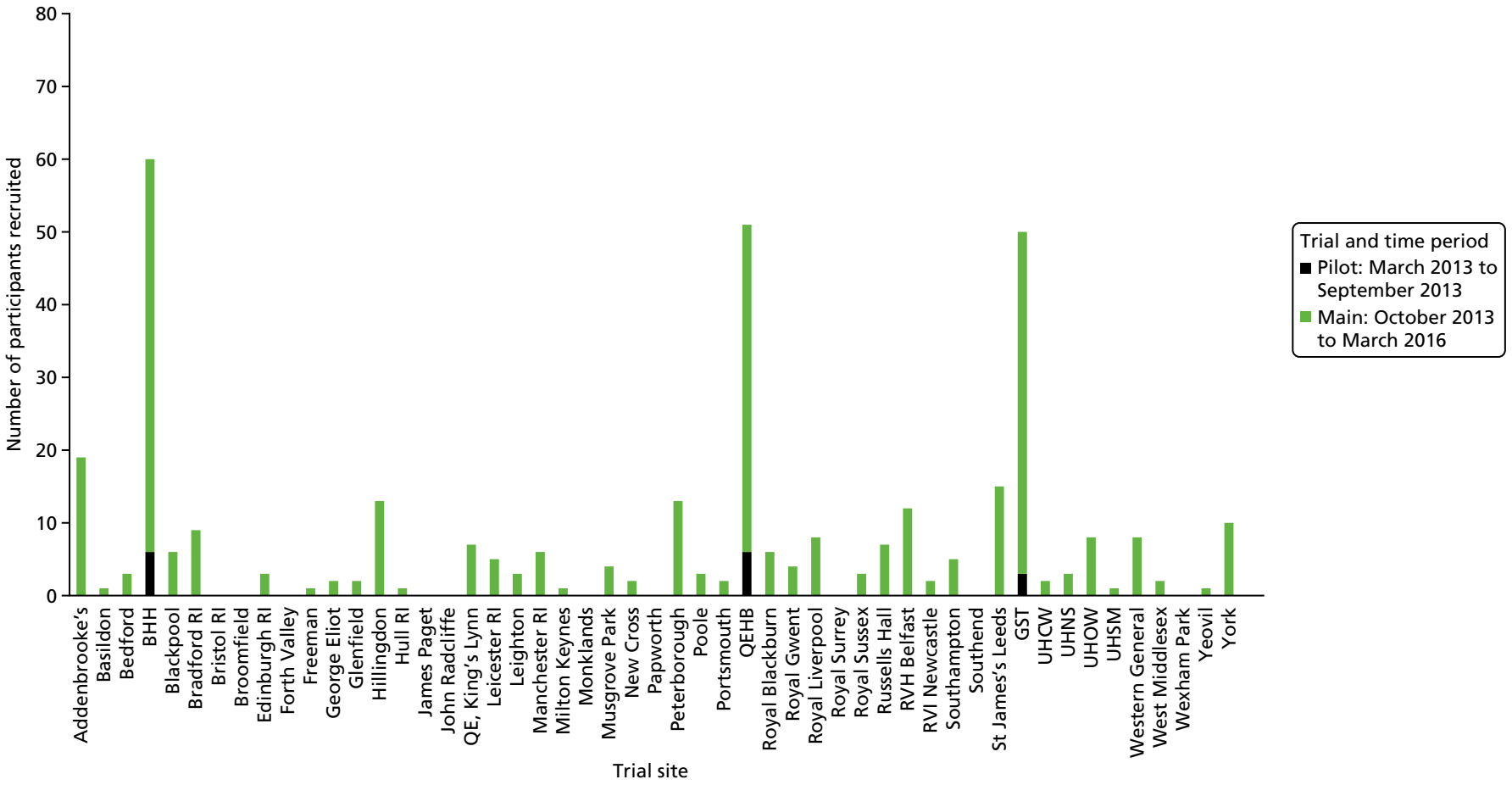


FIGURE 6 Participant recruitment by site. BHH, Birmingham Heartlands Hospital; GST, St Thomas' Hospital, London; QEHB, Queen Elizabeth Hospital, Birmingham; RI, Royal Infirmary; RVH, Royal Victoria Hospital; RVI, Royal Victoria Infirmary; UHCW, University Hospital Coventry and Warwickshire; UHNS, University Hospitals of North Midlands; UHOW, University Hospital of Wales; UHSM, University Hospital of South Manchester.

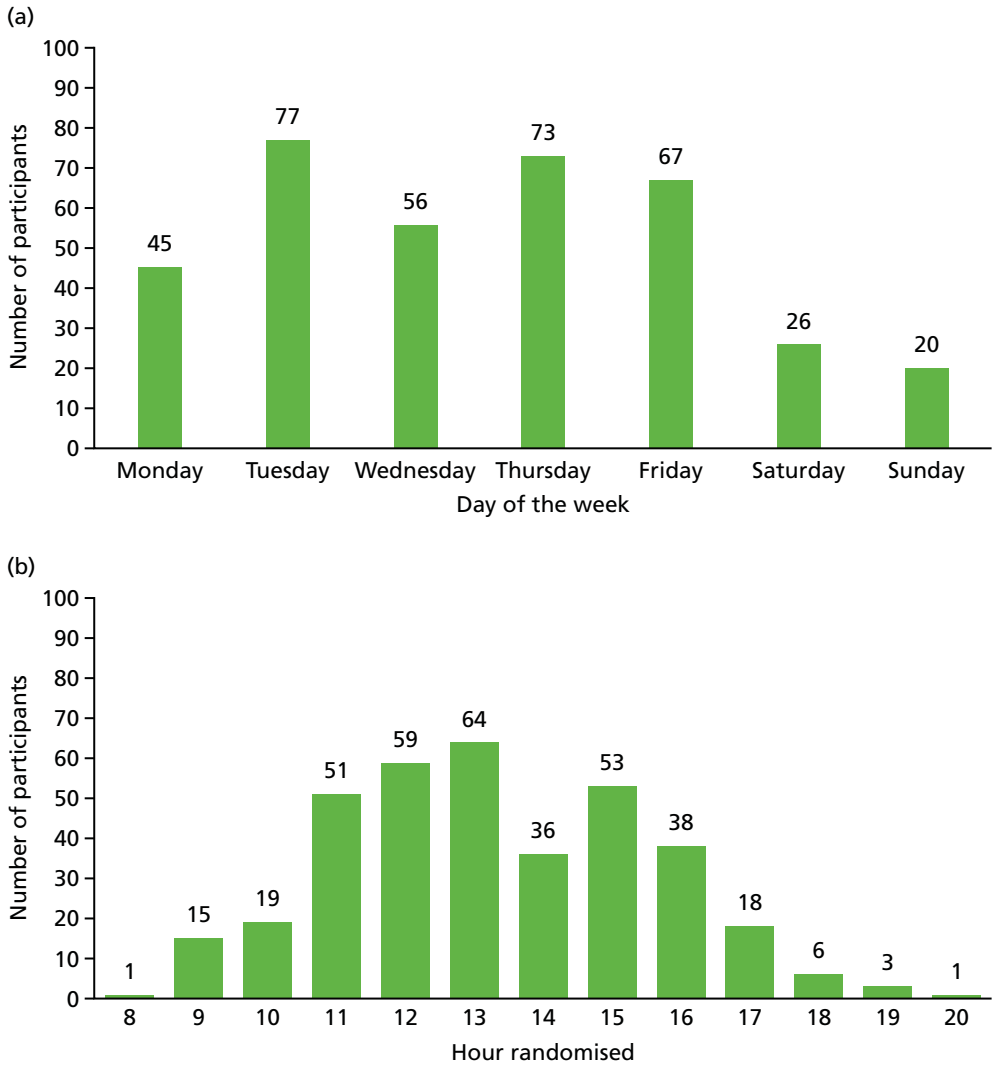


FIGURE 7 Randomisation of participants. (a) By day of the week; and (b) by time.

TABLE 6 Baseline demographic data of the trial participants

Characteristic	Trial group		
	Invasive weaning (*N* = 182)	Non-invasive weaning (*N* = 182)	Total (*N* = 364)
Age (years), mean (SD)	61.8 (15.8)	64.3 (13.6)	63.1 (14.8)
Sex (male), *n* (%)	94 (51.6)	90 (49.5)	184 (50.5)
Evidence of delirium (CAM-ICU result), *n* (%)			
Positive	17 (9.3)	23 (12.6)	40 (11.0)
Negative	132 (72.5)	130 (71.5)	262 (72.0)
Missing	33 (18.2)	29 (15.9)	62 (17.0)

continued

TABLE 6 Baseline demographic data of the trial participants (*continued*)

Characteristic	Trial group		
	Invasive weaning (*N* = 182)	Non-invasive weaning (*N* = 182)	Total (*N* = 364)
Height (cm)			
Mean (SD)	166.6 (10.7)	167.3 (10.5)	167.0 (10.6)
Missing (*n*)	4	4	8
Weight (kg)			
Mean (SD)	76.7 (18.8)	78.7 (19.7)	77.7 (19.3)
Missing (*n*)	0	1	1
BMI (kg/m^2)			
Mean (SD)	27.7 (6.6)	28.2 (6.9)	28.0 (6.7)
Missing (*n*)	4	5	9
Type of NIV interface used, *n* (%)			
Mask	1 (0.5)	174 (95.6)	175 (48.1)
Helmet	0	2 (1.1)	2 (0.5)
Not applicable	181 (99.5)	6 (3.3)	187 (51.4)
Duration of ventilation prior to randomisation (days), mean (SD)	5.3 (3.0)	6.3 (3.8)	5.8 (3.5)
APACHE II score			
Mean (SD)	18.8 (6.2)	18.9 (6.6)	18.9 (6.4)
Missing (*n*)	15	11	26
Diagnosis, *n* (%)			
Pneumonia/respiratory infection	73 (40.1)	57 (31.3)	130 (35.7)
COPD/asthma exacerbation	7 (3.9)	7 (3.9)	14 (3.8)
Non-respiratory infection	21 (11.5)	16 (8.8)	37 (10.2)
Traumatic injuries	5 (2.8)	3 (1.6)	8 (2.2)
Post-surgery respiratory failure	39 (21.4)	39 (21.4)	78 (21.4)
GI bleed	3 (1.7)	7 (3.9)	10 (2.8)
Cardiac	18 (9.9)	27 (14.8)	45 (12.4)
Neuromuscular	8 (4.4)	7 (3.9)	15 (4.1)
Overdose	0	4 (2.2)	4 (1.1)
Pancreatitis	0	4 (2.2)	4 (1.1)
Stroke	1 (0.5)	0	1 (0.3)
Other	7 (3.8)	11 (6.0)	18 (4.9)

GI, gastrointestinal.

TABLE 7 Baseline physiology data of the trial participants

SBT characteristics	Trial group		
	Invasive weaning ($n = 182$)	Non-invasive weaning ($n = 182$)	Total ($n = 364$)
Ventilation			
Exhaled minute volume (l per minute), mean (SD)	10.9 (3.6)	10.8 (3.9)	10.8 (3.8)
Total respiratory rate (breaths per minute), mean (SD)	22.5 (7.7)	22.1 (7.7)	22.3 (7.7)
PEEP (cmH_2O), mean (SD)	6.2 (1.6)	6.3 (2.0)	6.2 (1.8)
Plateau pressure (cmH_2O)			
Mean (SD)	17.4 (5.4)	18.0 (4.7)	17.7 (5.1)
Missing (*n*)	1	3	4
P_{supp} (cmH_2O)			
Mean (SD)	11.3 (5.2)	11.7 (4.3)	11.5 (4.8)
Missing (*n*)	1	3	4
$PaO_2 : FiO_2$ ratio (kPa)			
Mean (SD)	34.4 (11.3)	32.2 (9.2)	33.3 (10.4)
Missing (*n*)	1	1	2
Spontaneous tidal volume (ml/kg)			
Mean (SD)	8.6 (3.3)	8.6 (3.7)	8.6 (3.5)
Missing (*n*)	4	4	8
Haemodynamics			
Heart rate (beats per minute), mean (SD)	91.8 (19.8)	89.6 (18.9)	90.7 (19.3)
Systolic BP (mmHg), mean (SD)	135.0 (25.9)	137.7 (27.0)	136.4 (26.4)
Arterial blood gas			
PaO_2 (kPa)			
Mean (SD)	11.2 (2.5)	11.0 (2.7)	11.1 (2.6)
Missing (*n*)	1	1	2
$PaCO_2$ (kPa)			
Mean (SD)	5.7 (1.4)	5.7 (1.2)	5.7 (1.3)
Missing (*n*)	1	2	3
FiO_2			
Mean (SD)	0.34 (0.07)	0.35 (0.08)	0.35 (0.07)
Missing (*n*)	0	1	1
pH			
Mean (SD)	7.4 (0.06)	7.4 (0.06)	7.4 (0.06)
Missing (*n*)	5	7	12
H^+ (nmol)			
Mean (SD)	37.2 (2.9)	37.2 (2.0)	37.2 (2.3)
Missing (*n*)	177	176	353
Haemoglobin level (g/dl)			
Mean (SD)	9.7 (1.7)	9.6 (1.6)	9.6 (1.7)
Missing (*n*)	1	1	2

BP, blood pressure.

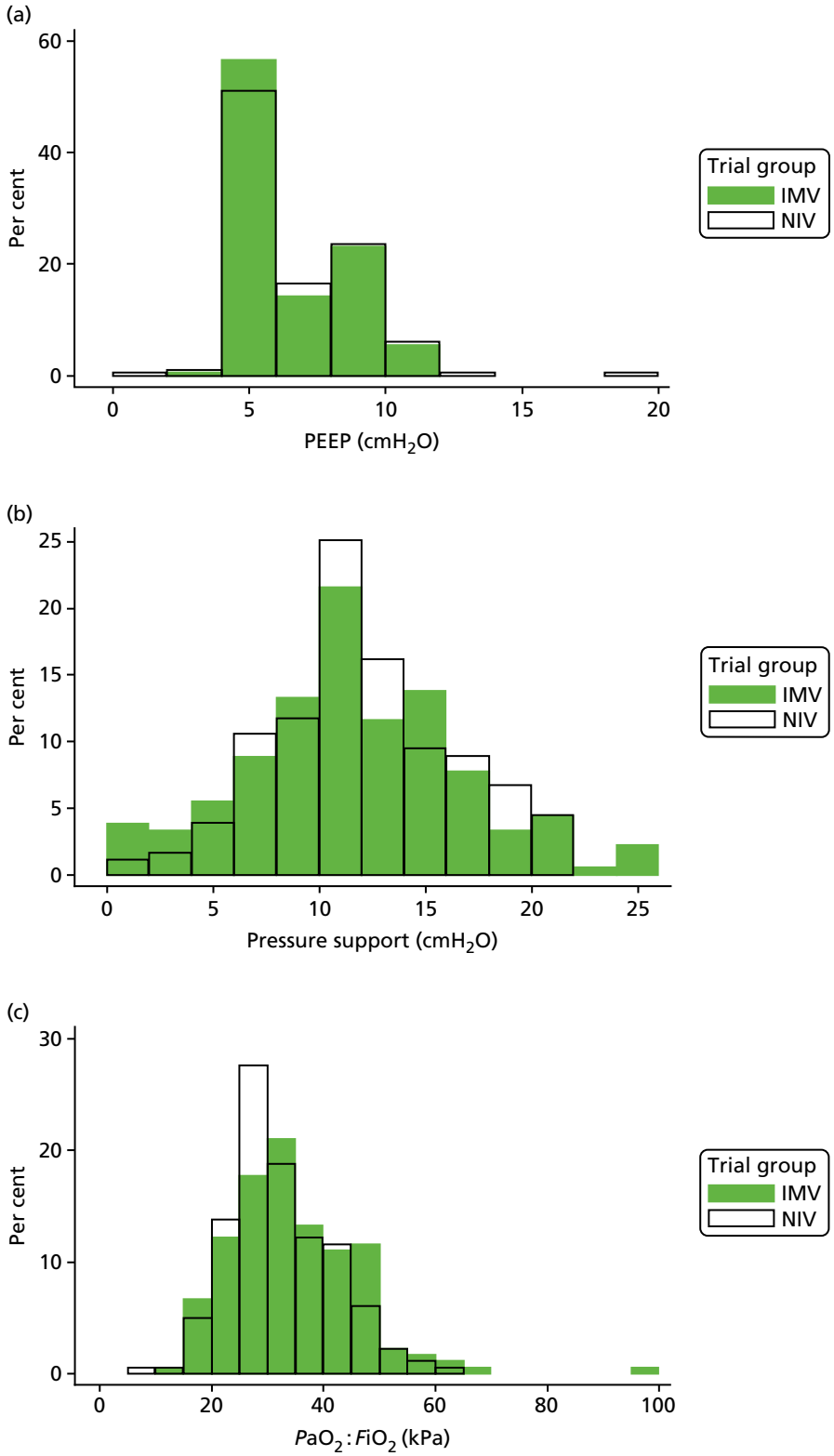


FIGURE 8 Distribution of baseline physiology data by treatment group. (a) PEEP; (b) P_{supp}; (c) $PaO_2 : FiO_2$ ratio; and (d) spontaneous tidal volume. (*continued*)

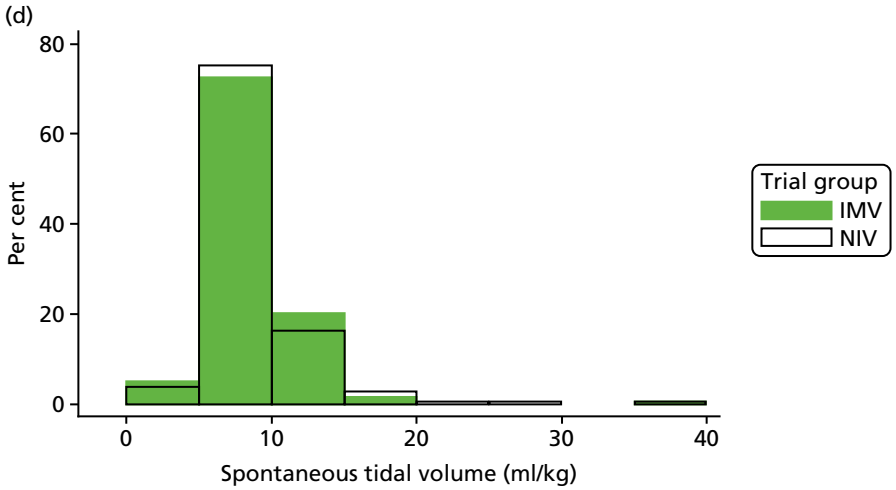


FIGURE 8 Distribution of baseline physiology data by treatment group. (a) PEEP; (b) P_{supp}; (c) $PaO_2 : FiO_2$ ratio; and (d) spontaneous tidal volume.

Participant baseline outcome measures

Participants who survived to hospital discharge were asked to rate their pre-admission quality of life. The pre-admission quality-of-life measurements were similar across the two groups (*Table 8*).

Participant spontaneous breathing trial characteristics

Table 9 summarises the participants' SBT characteristics along with reasons for failure. The majority of participants had CPAP (51.1%) or P_{supp} (32.7%) as the type of SBT performed, with an overall mean SBT duration of 47.4 minutes (SD 36.5 minutes). Most participants (73%) failed up to three of the criteria.

TABLE 8 Baseline health-related quality of life

Baseline measure	Trial group		Total
	Invasive weaning ($N = 182$)	Non-invasive ($N = 182$) weaning	($N = 364$)
EQ-5D-3L (prior to hospital admission)			
n	120	120	240
Mean (SD)	0.67 (0.37)	0.66 (0.35)	0.67 (0.36)
Median (IQR)	0.75 (0.52–1)	0.8 (0.52–1)	0.78 (0.52–1)
EQ VAS (today)			
n	119	115	234
Mean (SD)	58.7 (21.7)	60.8 (22.6)	59.7 (22.1)
Median (IQR)	60 (45–75)	60 (45–80)	60 (45–75)
SF-12 (mental)			
n	112	105	217
Mean (SD)	42.9 (13.4)	44.0 (12.9)	43.4 (13.1)
SF-12 (physical)			
n	112	105	217
Mean (SD)	37.3 (11.3)	37.2 (12.4)	37.2 (11.8)

EQ VAS, EuroQol visual analogue scale.
Note
The number of participants providing baseline summary data is low, primarily as a result of participants dying.

TABLE 9 Summary of the participants' SBT characteristics and reasons for failure

SBT charateristics	Trial group		
	Invasive weaning ($N = 182$)	Non-invasive weaning ($N = 182$)	Total ($N = 364$)
Type of SBT performed, *n* (%)			
T-piece	21 (11.5)	20 (11.0)	41 (11.3)
CPAP	94 (51.6)	92 (50.5)	186 (51.1)
P_{supp}	58 (31.9)	61 (33.5)	119 (32.7)
Missing	9 (5.0)	9 (5.0)	18 (4.9)
Duration of SBT (minutes)			
Mean (SD)	46.3 (35.3)	48.5 (37.8)	47.4 (36.5)
Missing	6	6	12
Number of criteria failed, *n* (%)			
1	37 (20.3)	32 (17.6)	69 (19.0)
2	42 (23.1)	56 (30.8)	98 (26.9)
3	49 (26.9)	48 (26.4)	97 (26.7)
4	24 (13.3)	18 (9.9)	42 (11.5)
5	18 (9.9)	15 (8.2)	33 (9.1)
6	6 (3.3)	8 (4.4)	14 (3.8)
7	3 (1.6)	4 (2.2)	7 (1.9)
8	3 (1.6)	1 (0.5)	4 (1.1)
Failed physiological assessments, *n* (%)			
Heart rate of > 20% of baseline or > 140 beats per minute	56 (30.8)	34 (18.7)	90 (24.7)
Systolic blood pressure of > 20% of baseline or > 180 mmHg or < 90 mmHg	55 (30.2)	65 (35.7)	120 (33.0)
Cardiac arrhythmias	4 (2.2)	5 (2.8)	9 (2.5)
Respiratory rate of ≥ 50% of baseline value or > 35 breaths per minute	109 (60.0)	106 (58.2)	215 (59.1)
Respiratory rate (breaths per minute)/tidal volume (l) of > 105 breaths per minute per l	30 (16.5)	23 (12.6)	53 (14.6)
Failed on arterial blood gases, *n* (%)			
PaO_2 of < 8 kPa on FiO_2 of > 0.5 or SpO_2 of < 90%	28 (15.4)	33 (18.1)	61 (16.8)
$PaCO_2$ of > 6.5 kPa or increase by > 1 kPa	24 (13.2)	22 (12.1)	46 (12.6)
pH of < 7.32 or a reduction in pH of > 0.07	11 (6.0)	13 (7.1)	24 (6.6)
Failed clinical assessment, *n* (%)			
Agitation and anxiety	76 (41.8)	79 (43.4)	155 (42.6)
Depressed mental status	12 (6.6)	3 (1.7)	15 (4.1)
Sweating/clammy	43 (23.6)	45 (24.7)	88 (24.2)
Cyanosis	3 (1.7)	1 (0.6)	4 (1.1)
Increased respiratory effort (accessory muscle use, facial distress, dyspnoea)	84 (46.2)	90 (49.5)	174 (47.8)

Note
Patients can have multiple reasons for failing a SBT.

Compliance with allocated treatment

Compliance was defined as whether or not a participant received their allocated intervention up to the point of death, liberation, reintubation or tracheostomy (whichever came first). There was a high level of compliance in both groups: 86.8% (158/182) of the participants in the IMV group and 96.2% (175/182) in the NIV group received their allocated intervention after randomisation.

Participant follow-up

Mortality data were available on all participants at hospital discharge and, when possible, were collected during follow-up. During the study, 51% (186/364) and 49% (177/364) of the participants provided follow-up at 3 months and 6 months, respectively (see *Figure 4*). The proportion of participants providing follow-up was similar in both groups at each time point.

Withdrawals

A summary of the withdrawals during the trial is provided in *Table 10*. A total of 12.9% (47/364) of the participants withdrew completely, 0.6% (2/364) withdrew in the ICU/high-dependency unit (HDU) and 1.1% (4/364) withdrew while in hospital. Most participants were happy to provide data during their inpatient stay but requested to withdraw completely from follow-up post hospital discharge; hence, 11.3% (41/364) withdrew at follow-up. In addition, 1.9% (7/364) of the participants withdrew from intervention only but remained in the trial. The different components of the trial from which participants withdrew have been summarised in *Table 11*.

Outcomes and analyses

Primary outcome: time to liberation from ventilation

Table 12 presents a summary of the primary outcome data. The proportion of participants liberated from ventilation was similar in both groups, with 87.9% (160/182) liberated in the invasive weaning group and 87.4% (159/182) liberated in the non-invasive weaning group. Moreover, there was no evidence of a statistically significant difference in the number of hours from randomisation to liberation from ventilation with an adjusted HR of 1.10 (95% CI 0.89 to 1.39). *Figure 9* presents a Kaplan–Meier plot of the time to liberation from ventilation summarised by treatment group. *Figure 10* presents a Kaplan–Meier plot of time to liberation from ventilation summarised by treatment group focused on days 0–30.

TABLE 10 Summary of withdrawals during the trial

Timing of withdrawal	Trial group, *n* (%)		Total, *n* (%) (*N* = 364)
	Invasive weaning (*N* = 182)	Non-invasive weaning (*N* = 182)	
Withdrew from intervention only during inpatient stay	3 (1.7)	4 (2.2)	7 (1.9)
In ICU/HDU (from randomisation to ICU discharge)	2 (1.1)	0	2 (0.6)
In hospital (from ICU/HDU discharge to hospital discharge)	1 (0.6)	3 (1.7)	4 (1.1)
From hospital discharge to 3 months' follow-up	17 (9.3)	14 (7.7)	31 (8.5)
3–6 months' follow-up	4 (2.2)	6 (3.3)	10 (2.8)

HDU, high-dependency unit.

TABLE 11 Details of withdrawal during inpatient stay

Withdrawn from	Withdrawal decision made by	Trial group, *n* (%)		Total, *n* (%) (*N* = 364)
		Invasive weaning (*N* = 182)	Non-invasive weaning (*N* = 182)	
The protocolised weaning intervention	Participant	1 (0.5)	0 (0.0)	1 (0.3)
	Personal consultee/next of kin	3 (1.6)	2 (1.1)	5 (1.4)
	Clinical	2 (1.1)	2 (1.1)	4 (1.1)
Ongoing data collection during hospital admission	Participant	1 (0.5)	3 (1.6)	4 (1.1)
	Personal consultee/next of kin	2 (1.1)	0 (0.0)	2 (0.5)
	Clinical	0 (0.0)	0 (0.0)	0 (0.0)
Confirmation of status at 30, 90 and 180 days	Participant	3 (1.6)	4 (2.2)	7 (1.9)
	Personal consultee/next of kin	5 (2.7)	0 (0.0)	5 (1.4)
	Clinical	0 (0.0)	0 (0.0)	0 (0.0)
Contact for follow-up questionnaires	Participant	3 (1.6)	6 (3.3)	9 (2.5)
	Personal consultee/next of kin	5 (2.7)	0 (0.0)	5 (1.4)
	Clinical	0 (0.0)	0 (0.0)	0 (0.0)

Note
Participants could withdraw from one or more of the above.

TABLE 12 Summary of the primary outcome with estimated treatment effect

Number of hours from randomisation to liberation from ventilation	Trial group		Adjusted estimate (95% CI); *p*-value[a]
	Invasive weaning (*N* = 182)	Non-invasive weaning (*N* = 182)	
n[b]	182	182	HR 1.10 (0.89 to 1.39); 0.352
Median (IQR)	108 (57–351)	104.3 (34.5–297)	

a Model adjusted for age, sex, centre, presence/absence of COPD, non-operative/operative and post-SBT $PaCO_2$.
b Liberation status is missing for three participants. One participant moved to another hospital that was not a participating site; therefore, this information could not be collected. The other two participants withdrew from the study completely; hence, these data were not collected.

Secondary outcomes

Mortality at 30, 90 and 180 days

There was no statistically significant difference in the participants' mortality status at 30 days, 90 days and 180 days post randomisation (*Table 13*). The mortality status of participants at ICU discharge and hospital discharge is also presented in *Table 13*.

Duration of invasive mechanical ventilation and total ventilation days

The duration of IMV was 3.1 days (95% CI 0.51 to 5.75 days) fewer in the non-invasive weaning group than the invasive weaning group (*Table 14*). *Figure 11* presents a box-and-whisker plot of the IMV days and total ventilator days by treatment group.

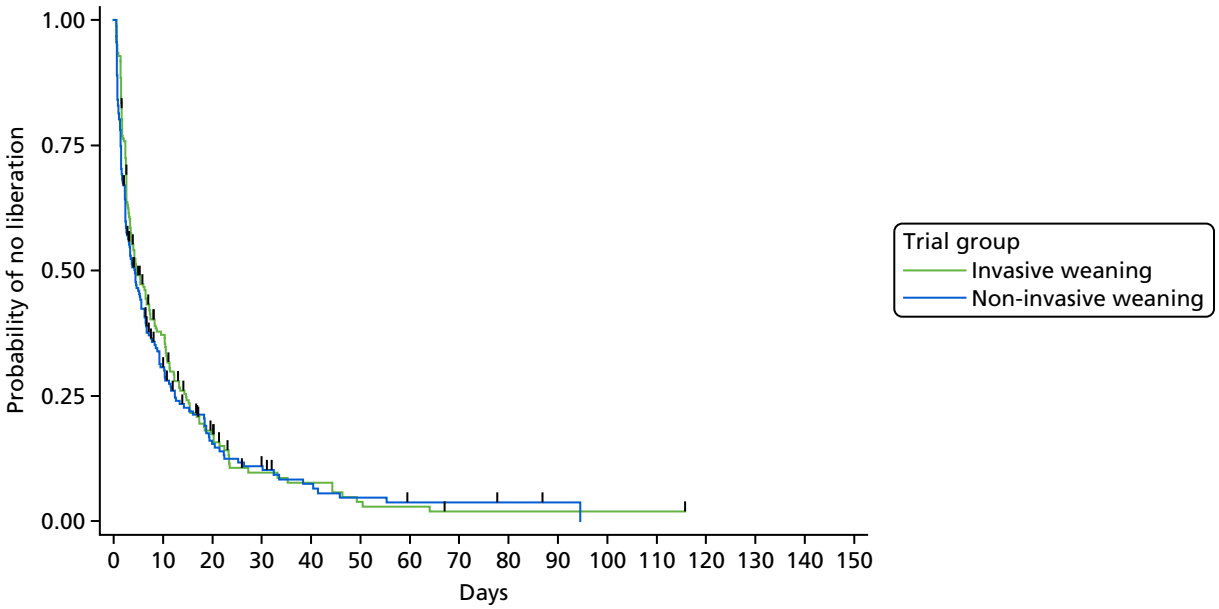


FIGURE 9 Kaplan–Meier curve of the time to liberation from ventilation by treatment group.

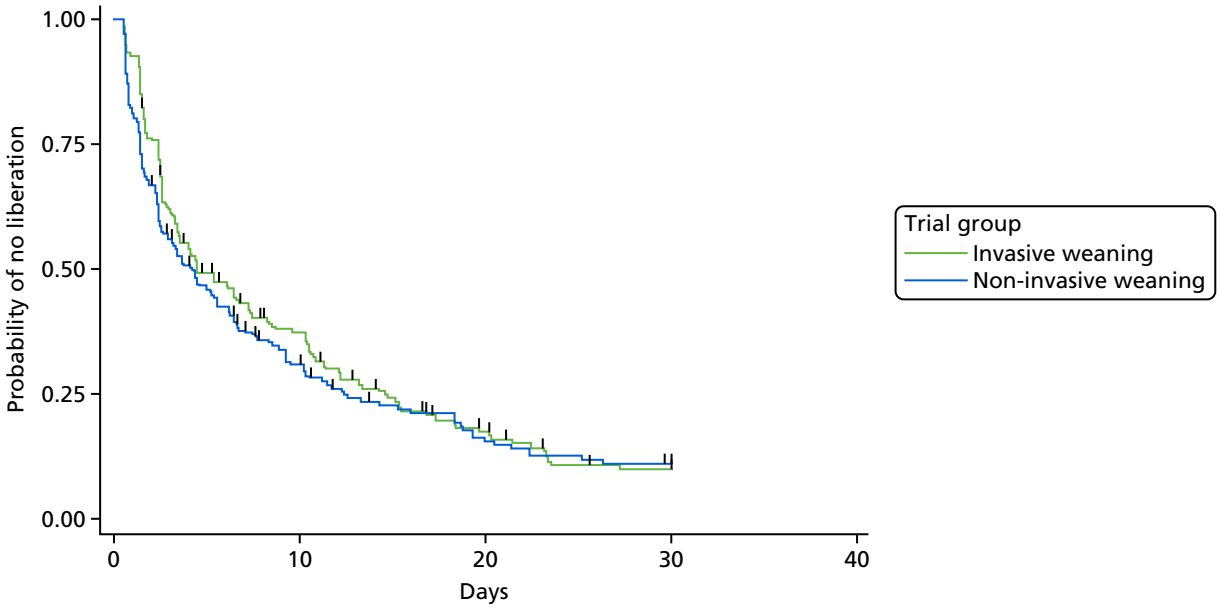


FIGURE 10 Kaplan–Meier curve of the time to liberation from ventilation by treatment group, focused on days 0–30.

TABLE 13 Mortality at 30, 90 and 180 days

Mortality	Trial group, *n* (%)		Adjusted OR (95% CI); *p*-value
	Invasive weaning (*N* = 182)	Non-invasive weaning (*N* = 182)	
30 days	157 (86.3)	158 (86.8)	0.90 (0.51 to 1.73); 0.856
90 days	137 (75.3)	142 (78.0)	0.80 (0.49 to 1.33); 0.393
180 days	134 (73.1)	142 (78.0)	0.70 (0.44 to 1.18); 0.189
ICU discharge	157 (86.3)	160 (87.9)	0.90 (0.48 to 1.70); 0.764
Hospital discharge	146 (80.2)	147 (80.8)	0.90 (0.54 to 1.58); 0.776

TABLE 14 Summary of the duration of IMV and total ventilator days

Outcome	Trial group		Adjusted IRR estimate (95% CI); *p*-value[a]	Adjusted mean difference (95% CI); *p*-value
	Invasive weaning (*n* = 182)	Non-invasive weaning (*n* = 182)		
Number of days on IMV				
Mean (SD)	9.1 (13.6)	6.0 (11.5)	0.6 (0.47 to 0.87); 0.005	–3.1 (–5.75 to –0.51); 0.019
Median (IQR)	4 (2–11)	1 (0–7)		
Total ventilator days (IMV and NIV)				
Mean (SD)	9.6 (13.8)	7.7 (11.5)	0.8 (0.62 to 1.00); 0.049	–2.0 (–4.61 to 0.69); 0.146
Median (IQR)	4 (2–12)	3 (1–9)		

a Model adjusted for age, sex, centre, presence/absence of COPD, non-operative/operative and post-SBT $PaCO_2$.

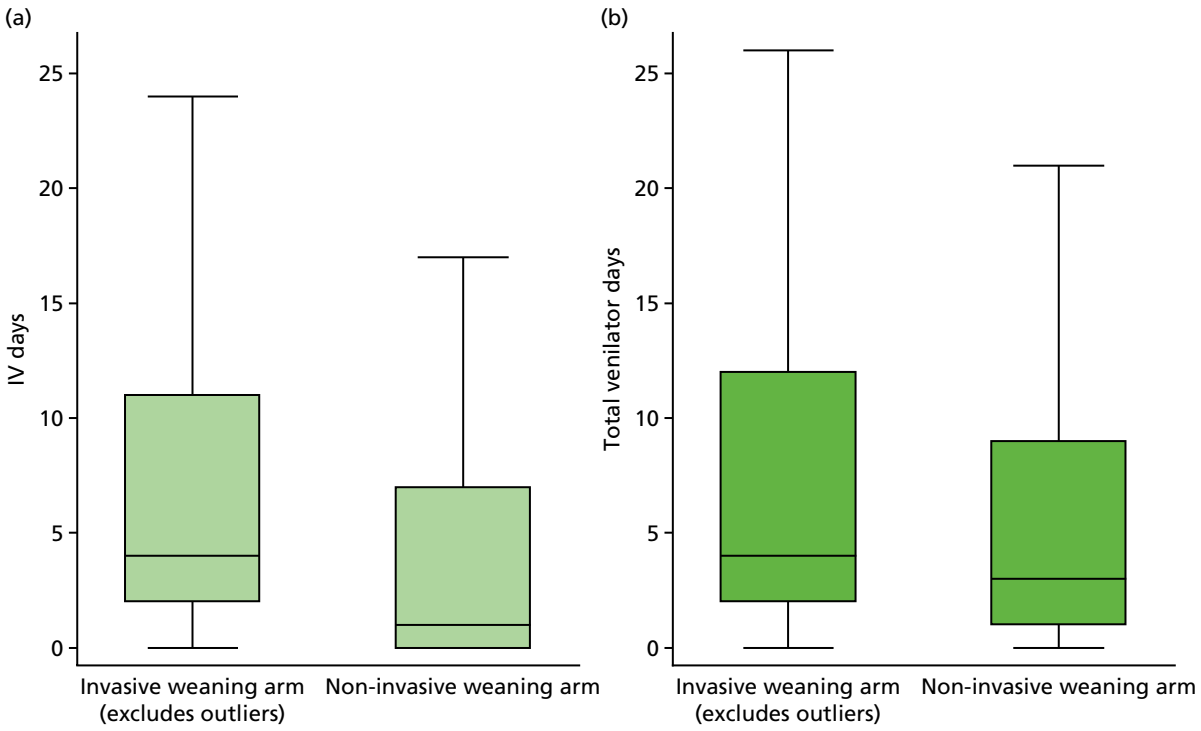


FIGURE 11 Box-and-whisker plots of IMV days and total ventilator days by treatment group. (a) IMV days; and (b) total ventilator days.

Antibiotics for respiratory infection and total antibiotic usage

Figure 12 presents a summary of the proportion of participants that required respiratory antibiotics as well as details of the total number of days of respiratory and non-respiratory antibiotic usage. A lower proportion of participants required respiratory antibiotics (OR 0.60, 95% CI 0.41 to 1.00) in the non-invasive weaning group compared with the invasive weaning group. There was no difference between the two groups in the total (respiratory and non-respiratory) number of days that antibiotics were used (IRR 0.90, 95% CI 0.68 to 1.08).

Reintubation and tracheostomy

There was a statistically significant difference in reintubation rates between the two groups (*Figure 13*) in which participants in the non-invasive weaning group were twice as likely to be reintubated at any time (OR 2.00, 95% CI 1.27 to 3.24). There was no difference in the tracheostomy rates between the two groups (OR 0.70, 95% CI 0.44 to 1.15).

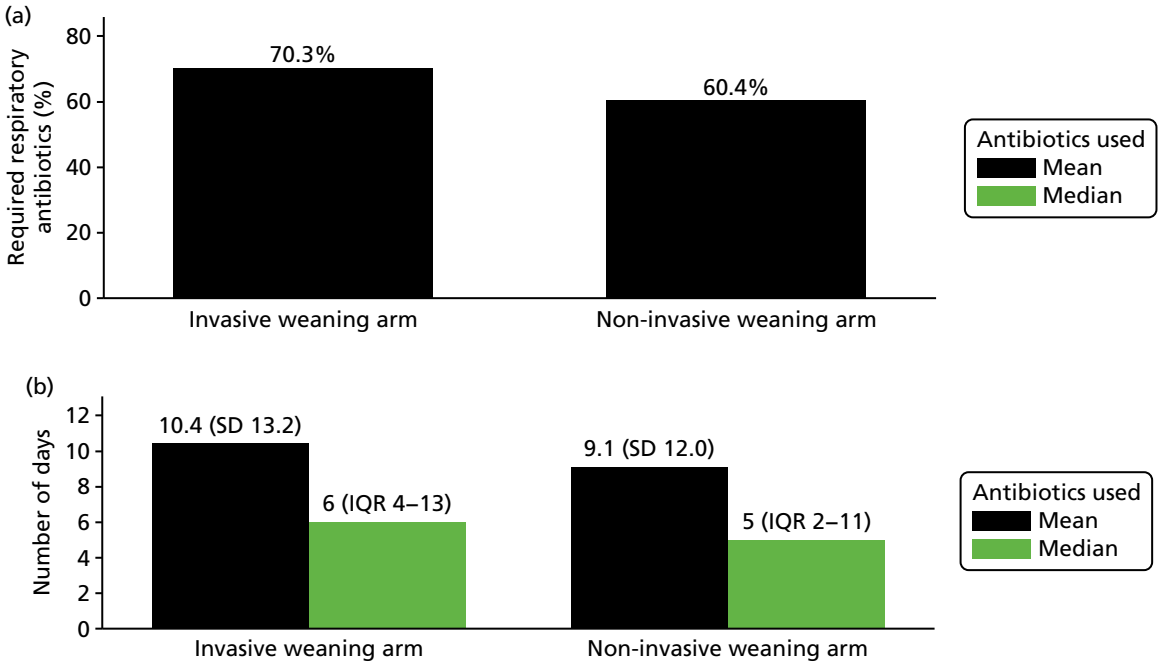


FIGURE 12 Respiratory antibiotic and total antibiotic usage summarised by treatment group. (a) Respiratory antibiotic usage; and (b) total number of days of antibiotic usage.

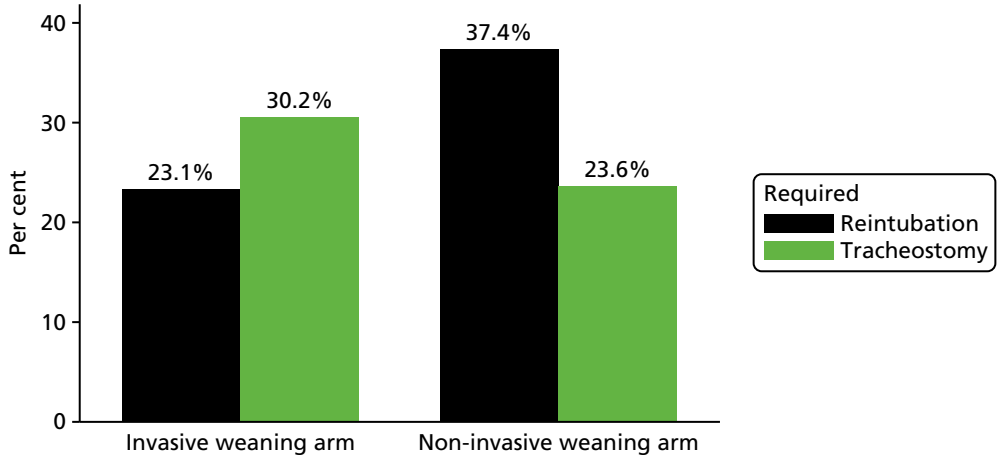


FIGURE 13 Reintubation and tracheostomy rates summarised by treatment group.

Time to meeting intensive care unit discharge criteria

The length of time (in days) until meeting ICU discharge criteria was similar between both groups (HR 1.10, 95% CI 0.91 to 1.42). *Figure 14* presents a Kaplan–Meier plot of the time to meeting discharge criteria.

Process variables

A number of process variables were explored to provide a richer understanding of the weaning process and to enable the findings of the Breathe trial to be incorporated into future meta-analyses. This included time to extubation, sedative use, duration of organ support, duration of critical care stay and weaning failure.

Time to extubation

As expected, there is evidence of a significant difference in the time (days) from randomisation to extubation (HR 2.50, 95% CI 1.99 to 3.12): participants had a median time of 0.5 days (IQR 0.5–1 day) in the NIV group compared with a median time of 3 days (IQR 2–10 days) in the IMV group. *Figure 15* presents a Kaplan–Meier plot for the time to being extubated.

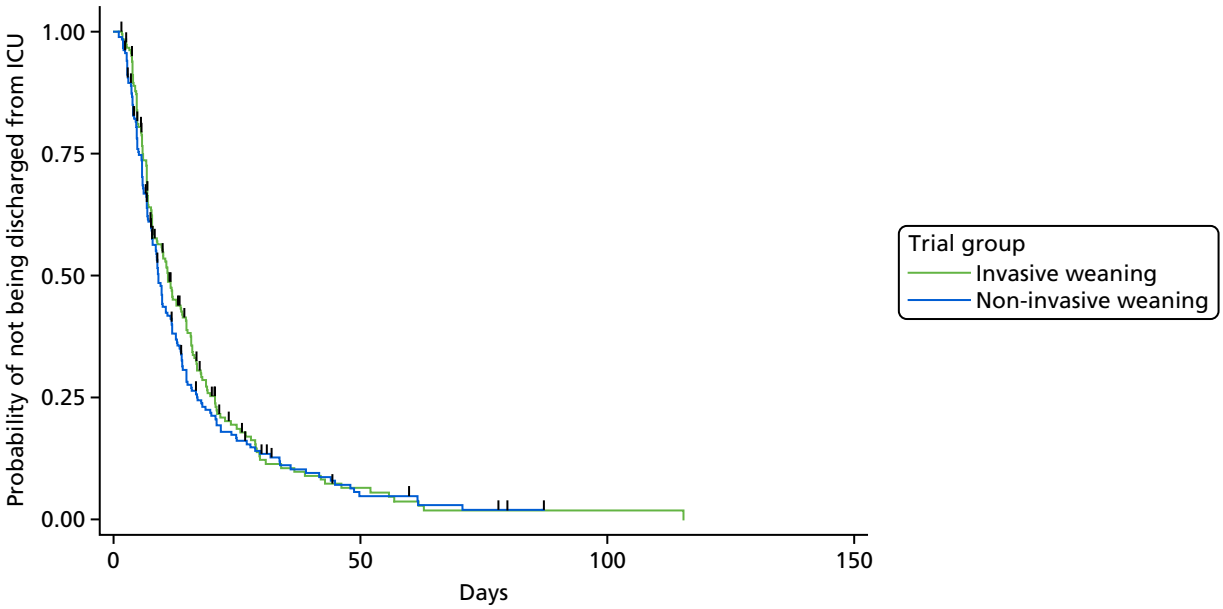


FIGURE 14 Kaplan–Meier plot of the time to meeting discharge criteria.

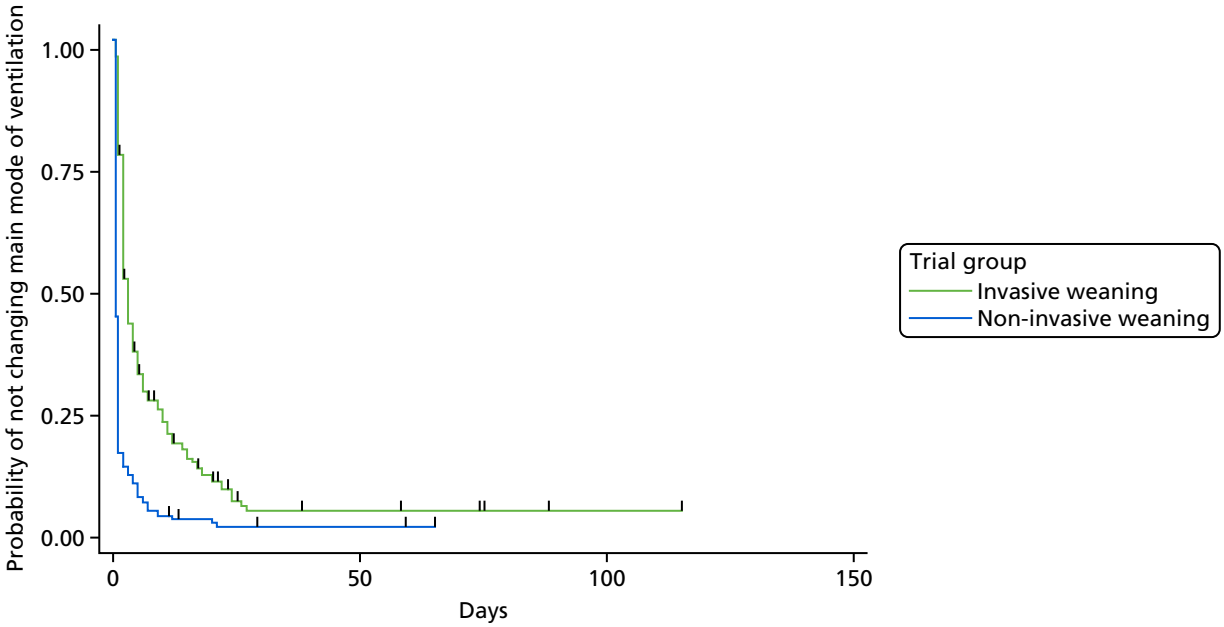


FIGURE 15 Kaplan–Meier curve for the time from randomisation to extubation.

Sedative use, support/organ monitoring and care status

Table 15 presents a summary of the participants' sedative use, support/organ monitoring and care status by treatment group. Compared with the invasive weaning group, participants in the non-invasive weaning group required fewer days on one or more class of sedative (IRR 0.7, 95% CI 0.60 to 0.90), fewer days on advanced respiratory support (IRR 0.7, 95% CI 0.51 to 0.90) and more days on basic respiratory support (IRR 1.3, 95% CI 1.04 to 1.51). There was no difference between the two groups in the number of days on advanced cardiovascular support, basic cardiovascular support or renal support. There was evidence of a significant difference in the number of days participants required level 2/3 care with participants in the non-invasive weaning group requiring fewer days of level 2/3 care than those in the invasive weaning group ($p = 0.024$).

TABLE 15 Summary of sedative use, support/organ monitoring data and care status

Outcomes	Trial group		
	Invasive weaning ($n = 182$)	Non-invasive weaning ($n = 182$)	Adjusted IRR estimate (95% CI); p-value[a]
Number of days participant on one or more class of sedative			
Mean (SD)	5.5 (5.1)	4.1 (5.0)	0.7 (0.60 to 0.90); 0.003
Median (IQR)	3 (2–8)	2 (1–5)	
Number of days participant on advanced respiratory support			
Mean (SD)	9.4 (13.7)	6.5 (11.7)	0.7 (0.51 to 0.90); 0.007
Median (IQR)	4 (2–13)	1 (0– 7)	
Number of days participant on basic respiratory support			
Mean (SD)	4.1 (4.5)	5.3 (5.6)	1.3 (1.04 to 1.51); 0.019
Median (IQR)	3 (1–6)	4 (2–7)	
Number of days participant on advanced cardiovascular support			
Mean (SD)	1.1 (3.1)	0.6 (1.6)	0.6 (0.30 to 1.07); 0.081
Median (IQR)	0 (0–0)	0 (0–0)	
Number of days participant on basic cardiovascular support			
Mean (SD)	11.3 (13.0)	10.0 (10.8)	0.9 (0.71 to 1.04); 0.129
Median (IQR)	7 (5–14)	6.5 (4–13)	
Number of days participant on renal support			
Mean (SD)	2.1 (8.1)	1.7 (5.2)	1.0 (0.45 to 2.06); 0.919
Median (IQR)	0 (0–0)	0 (0–0)	
Number of days participant at care level 2 or 3			
Mean (SD)	12.2 (8.4)	10.8 (8.8)	0.024
Median (IQR)	10 (5–17)	7.5 (4–14)	

a A negative binomial model was used to estimate the adjusted IRR effect sizes; otherwise, only the p-value is presented from a non-parametric Wilcoxon rank-sum test. Model adjusted for age, sex, centre, presence/absence of COPD, non-operative/operative and post-SBT $PaCO_2$.

Weaning failure

Weaning failure, which was defined as reintubation within 48 hours of extubation, or as death (day 0–7), tracheostomy (day 0–7) or on IMV (on day 7), has been summarised in *Table 16*. There was no evidence of a difference between the two groups for either definition of weaning failure.

Reintubation

The median time from randomisation to reintubation was significantly shorter ($p < 0.001$) in the non-invasive weaning group than in the invasive weaning group (*Table 17*) [invasive weaning, 3.2 days (IQR 2.3–4.7 days), vs. non-invasive weaning, 2 days (IQR 0.9–3.0 days)]. There was no difference in the final outcome of those participants who were reintubated.

TABLE 16 Summary of weaning failure by treatment group

Outcome	Trial group, *n* (%)		Adjusted OR estimate (95% CI); *p*-value[a]
	Invasive weaning (*N* = 182)	Non-invasive weaning (*N* = 182)	
Weaning failure: reintubation within 48 hours of extubation			
No	174 (95.6)	165 (90.7)	2.30 (0.96 to 5.61); 0.063
Yes	8 (4.4)	17 (9.3)	
Weaning failure: death (day 0–7), tracheostomy (day 0–7) or on IMV (on day 7)			
No	109 (89.9)	123 (67.6)	0.70 (0.48 to 1.13); 0.163
Yes	73 (40.1)	59 (32.4)	

a Model adjusted for age, sex, centre, presence/absence of COPD, non-operative/operative and post-SBT $PaCO_2$.

TABLE 17 Summary of the time to reintubation and final outcome of those reintubated

Outcome	Trial group		Adjusted estimate (95% CI); *p*-value[a]
	Invasive weaning (*N* = 182)	Non-invasive weaning (*N* = 182)	
Time from randomisation to reintubation (days)			
n	42	68	< 0.001
Mean (SD)	4.0 (3.0)	2.7 (2.7)	
Median (IQR)	3.2 (2.3–4.7)	2 (0.9–3.0)	
Final outcome of those reintubated, *n* (%)			
Liberated	34 (80.9)	51 (75.0)	OR 1.40 (0.43 to 4.26); 0.601
Died	6 (14.3)	16 (23.5)	
Missing	2 (4.8)	1 (1.5)	

a Model adjusted for age, sex, centre, presence/absence of COPD, non-operative/operative and post-SBT $PaCO_2$. Only a *p*-value is presented from a non-parametric Wilcoxon rank-sum test when data are non-normal.

Intensive care unit/high-dependency unit and hospital discharge data

Table 18 presents a summary of the ICU/HDU and hospital discharge data. There were no differences found in the discharge data between the two groups. Approximately 87% of the participants were discharged alive from ICU/HDU, most of whom were discharged to a ward. Approximately 80% of the participants were discharged alive from hospital, with most (74%) of the participants returning home.

Adverse events

The AE data have been detailed in *Table 19*. Approximately 25% of the participants in each group experienced a new AE during their ICU stay. There was no difference between the two groups in the number of days for which new AEs were reported or in the type of event reported.

Serious adverse events

The SAEs reported during the trial have been detailed in *Table 20*. In total, 42 SAEs were reported: 16 in the invasive weaning group and 26 in the non-invasive weaning group. Most of the reported SAEs were unrelated to the trial intervention.

TABLE 18 Summary of ICU/HDU and hospital discharge data

Outcomes	Trial group		
	Invasive weaning ($N = 182$)	Non-invasive weaning ($N = 182$)	p-value[a]
Discharged alive from ICU/HDU (yes), *n* (%)	157 (86.3)	160 (87.9)	0.842
Discharged location from ICU, *n* (%)			
Ward	150 (95.5)	153 (95.6)	0.246
Other critical care facility	3 (1.9)	6 (3.8)	
Other	4 (2.6)	1 (0.6)	
Discharged alive from hospital (yes), *n* (%)	145 (79.7)	146 (80.2)	0.896
Discharged location from hospital, *n* (%)			
Home	108 (74.5)	108 (72.6)	0.231
Rehabilitation	8 (5.5)	8 (5.5)	
Other	9 (6.2)	3 (2.0)	
Nursing/residential home	4 (2.8)	10 (6.9)	
Another hospital	16 (11.0)	18 (12.3)	
Time from ICU admission to hospital discharge (days)			
n	145	146	0.558
Mean (SD)	41.0 (39.9)	40.8 (28.6)	
Median (IQR)	31.9 (18.9–31.9)	32.6 (21.9–51.8)	

a The p-value was computed using either the chi-squared test or the Fisher's exact test for categorical data and the Wilcoxon rank-sum test for continuous non-normal data.

TABLE 19 Summary of new adverse events reported

Outcomes	Trial group		
	Invasive weaning ($N = 182$)	Non-invasive weaning ($N = 182$)	Adjusted estimate (95% CI); p-value[a]
Number of days new AEs reported			
Mean (SD)	0.5 (1.2)	0.6 (1.4)	IRR 1.20 (0.71 to 1.92); 0.538
Median (IQR)	0 (0–1)	0 (0–0)	
Participant experienced new AE (yes), *n* (%)	47 (25.8)	45 (24.7)	OR 0.90 (0.57 to 1.49); 0.739
Type of new AE reported, *n* (%)[b]			
Nasal/skin/mouth sores/irritation	14 (7.7)	19 (10.4)	OR 1.30 (0.64 to 2.82); 0.433
Vomiting	8 (4.4)	14 (7.7)	OR 1.90 (0.76 to 4.62); 0.173
Gastric distension	6 (3.3)	7 (3.9)	OR 1.00 (0.32 to 3.25); 0.964
Barotrauma (e.g. pneumothorax)	3 (1.7)	3 (1.7)	OR 1.40 (0.25 to 7.43); 0.725
Non-respiratory infection	12 (6.6)	11 (6.0)	OR 0.80 (0.35 to 2.00); 0.691
Arrhythmia	22 (12.1)	14 (7.7)	OR 0.60 (0.29 to 1.22); 0.156

a The model was adjusted for age, sex, centre, presence/absence of COPD, non-operative/operative and post-SBT $PaCO_2$.
b Each type of AE has been summarised separately for all participants, as participants can report one or more new AE types.

TABLE 20 Summary of SAEs reported

Outcomes	Trial group, *n* (%)	
	Invasive weaning	Non-invasive weaning
	Events (*N* = 16)	Events (*N* = 26)
Event type		
Death	3 (18.8)	5 (19.2)
Life-threatening	8 (50.0)	13 (50.0)
Hospitalisation or prolongation of existing hospitalisation	10 (62.5)	10 (38.5)
Persistent or significant disability/incapacity	1 (6.3)	2 (7.7)
Congenital anomaly/birth defect	0 (0.0)	0 (0.0)
Other reason	2 (12.5)	4 (15.4)
Event related to trial intervention (in the opinion of the reporting clinician)		
Definitely	1 (6.3)	0 (0.0)
Probably	0 (0.0)	0 (0.0)
Possibly	0 (0.0)	4 (15.4)
Unlikely	2 (12.5)	6 (23.1)
Unrelated	10 (62.5)	16 (61.5)
Missing	3 (18.7)	0 (0.0)
Event expectedness		
Expected	1 (6.2)	1 (3.9)
Unexpected	0 (0.0)	3 (11.5)
Not applicable	15 (93.8)	22 (84.6)
Outcome of event		
Resolved – no sequelae	6 (37.6)	10 (38.5)
Resolved – with sequelae	4 (25.0)	3 (11.5)
Unresolved	3 (18.7)	4 (15.4)
Death	3 (18.8)	9 (34.6)

Health-related quality of life

A summary of the HRQoL of participants at follow-up is presented in *Table 21*. There were no differences found between the two groups in terms of their reported quality of life.

Subgroup analyses

The results of the prespecified (i.e. COPD status and operative status) and exploratory (i.e. site and P_{supp}) subgroup analyses are presented in *Table 22*. None of the explored subgroups showed evidence of a moderating treatment effect.

TABLE 21 Summary of the HRQoL data

Outcomes	Trial group		Adjusted estimate (95% CI); *p*-value[a]
	Invasive weaning (*N* = 182)	Non-invasive weaning (*N* = 182)	
EQ-5D-3L change			
Baseline to 3 months			
n	81	81	0.01 (–0.12 to 0.14); 0.920
Mean (SD)	0.13 (0.40)	0.14 (0.42)	
Baseline to 6 months			
n	74	81	0.08 (–0.05 to 0.21); 0.215
Mean (SD)	0.04 (0.38)	0.14 (0.40)	
EQ VAS			
3 months			
n	91	92	–0.5 (–6.77 to 5.84); 0.885
Mean (SD)	62.5 (20.2)	60.9 (20.0)	
6 months			
n	82	91	–2.8 (–9.45 to 3.93); 0.417
Mean (SD)	65.0 (21.2)	61.7 (22.4)	
SF-12 (mental)			
3 months			
n	80	82	–1.0 (–4.92 to 2.83); 0.594
Mean (SD)	45.8 (10.9)	43.8 (12.6)	
6 months			
n	75	84	–0.3 (–4.62 to 4.00); 0.888
Mean (SD)	45.4 (13.3)	44.7 (12.1)	
SF-12 (physical)			
3 months			
n	80	82	–0.4 (–3.81 to 3.01); 0.815
Mean (SD)	33.7 (9.7)	33.4 (10.3)	
6 months			
n	75	84	–1.3 (–4.95 to 2.43); 0.499
Mean (SD)	37.0 (10.4)	35.5 (11.6)	

EQ VAS, EuroQol visual analogue scale.
a Model adjusted for age, sex, centre, presence/absence of COPD, non-operative/operative and post-SBT $PaCO_2$.

TABLE 22 Subgroup analyses results

Subgroups	Trial group, *n*; median (IQR)		Effect (95% CI); *p*-value[a]	
	Invasive weaning	Non-invasive weaning	Within-group treatment	Interaction
COPD status				
Absence of COPD	150; 108 (57.9–322.3)	151; 91 (34–301.7)	HR 1.10 (0.85 to 1.39); 0.517	HR 1.20 (0.63 to 2.12); 0.640
Presence of COPD	32; 128 (38–442)	31; 107.6 (45.7–269)	HR 1.40 (0.78 to 2.59); 0.252	
Operative status				
Non-operative	126; 156.2 (58.5–416)	126; 111.5 (41–276)	HR 1.20 (0.94 to 1.64); 0.124	HR 0.70 (0.45 to 1.21); 0.231
Postoperative	56; 85.5 (35.4–255.5)	56; 57 (18.5–442)	HR 1.00 (0.63 to 1.44); 0.816	
Three main sites vs. other				
Three main sites	82; 128 (40–273)	79; 83 (32–297)	HR 1.00 (0.73 to 1.44); 0.899	HR 1.20 (0.76 to 1.87); 0.438
Other	100; 108 (59.7–472.6)	103; 107 (35–301.7)	HR 1.20 (0.89 to 1.64); 0.218	
P_{supp} (cmH_2O)				
< 10	63; 79 (38–259)	52; 42 (18–320)	HR 1.10 (0.73 to 1.62); 0.674	HR 1.10 (0.67 to 1.76); 0.731
≥ 10	118; 174 (58–370)	127; 125 (54–297)	HR 1.10 (0.84 to 1.47); 0.443	

a Model adjusted for age, sex, centre, presence/absence of COPD, non-operative/operative and post-SBT $PaCO_2$.

Sensitivity analysis

Adjustment for baseline pneumonia

There was some indication of a difference between the two groups in the number of participants diagnosed with pneumonia/respiratory infection at baseline. A sensitivity analysis was undertaken but no difference was found (HR 1.10, 95% CI 0.88 to 1.38).

Per-protocol analysis

A per-protocol sensitivity analysis was undertaken to estimate the treatment effect, having excluded protocol violators, to see if the treatment effect estimates differed from the primary analysis results. The results of the sensitivity analysis were similar to those of the primary analysis results, which suggested that there was no difference between the two groups (HR 1.10, 95% CI 0.89 to 1.43).

Chapter 5 Economic evaluation

Overview of the economic evaluation

This prospective economic evaluation was conducted alongside a pragmatic, randomised, controlled, open, multicentre, effectiveness trial (Breathe RCT) with the objective of estimating the cost-effectiveness of IMV using protocolised weaning that includes NIV as an intermediate step compared with protocolised weaning without NIV. Patients with respiratory failure who received IMV for > 48 hours (from the time of intubation) and failed a SBT were randomised in a 1 : 1 ratio to either the invasive or the non-invasive weaning strategy. The economic evaluation took the form of a cost–utility analysis, expressed in terms of incremental cost per QALY gained. The primary analysis is based on both a NHS and PSS perspective as recommended by NICE, and excludes costs borne by sectors of the economy other than the health and social service sectors, and costs borne by trial participants and their families/informal carers.[35] Costs are expressed in Great British pounds (GBP) (2015–16 prices). A sensitivity analysis was conducted to recalculate cost-effectiveness from a societal perspective.

Measurement of resource use and costs

The incremental costs associated with the NIV strategy were determined through a comprehensive strategy that encompassed two strands of research: (1) estimation of costs associated with the delivery of the intervention and (2) estimation of broader health and PSS resource inputs and costs.

Resource use associated with non-invasive ventilation (intervention)

A specific focus of the economic evaluation was the assessment of hospital resource inputs associated with delivering the NIV intervention. This was based on data associated with ICU-related length of stay for organ support (advanced or basic cardiovascular or respiratory support, renal support, dermatological support, antimicrobial use, whether respiratory or non-respiratory) collected from randomisation on a daily basis for the first 30 days during a participant's stay in ICU. In addition, daily data on the highest level of care (levels 0, 1, 2 or 3) over each 24-hour period over the first 30 days during the ICU stay and on use of antibiotics, sedatives and antiviral medications were collected. Similarly, hospital resource use data were also collected beyond the first 30 days, including the nature of respiratory support (advanced or basic), renal support, dermatological support and antimicrobial use (respiratory or non-respiratory) up to ICU discharge. Furthermore, data on the length and intensity of hospital stay, post ICU discharge until final hospital discharge, were collected; details of hospital transfers between the hospital at randomisation and other hospitals (or residence) were also included. Information on the use of high-cost medications was collected on a daily basis.

Collection of broader resource use data

Health and social service resource use data were collected at 3 and 6 months post randomisation, using self-completed postal questionnaires. Postal reminders were sent to non-responders and, when required, further telephone contacts when made to encourage the return of questionnaires or to request the completion of missing data. The postal questionnaires provided details on the frequency and duration of use of hospital inpatient care (including readmissions), hospital outpatient care, residential care services, community health and social care services, medications and any equipment or aids that were needed by participants. Medication use was categorised by drug name (or active constituent), mode of administration, dosage frequency and duration of administration. Health and social care resource inputs were subsequently converted into economic cost estimates using unit cost data. For broader societal resource impacts, the actual costs incurred by participants and their families and carers for items such as travel, child care and lost income were valued directly by trial participants and recorded on the data collection forms in monetary terms.

Valuation of resource use

Resource inputs were valued using a combination of primary research and data collated from secondary national tariff sets, using standard accounting methods. For ICU-related resource inputs, the overall costs of intensive care were derived using individual-level data on the number of days of each form of organ support, the number of days of each level of intensive care and the overall duration of the intensive care stay. These patient-level data on duration, number and type of organ support, the duration and level of intensive care and the overall duration of the intensive care stay were used as inputs to generate Healthcare Resource Group (HRG) codes that were subsequently valued using *NHS Reference Costs 2014 to 2015*.[36] Each ICU-related HRG code is associated with a mean length of hospital stay. For all individuals in the ICU, costs were determined over their length of stay for their derived HRG code.

The unit costs of high-cost drugs not included within ICU-specific HRG values (e.g. antifungals and antivirals) were taken from the *Prescription Cost Analysis – England, 2016* database.[37] The unit costs associated with hospital readmissions, hospital day-case admissions, hospital outpatient services costs and accident and emergency attendances were extracted from NHS reference costs[36] or, when necessary, the unit cost compendia published by the Personal Social Services Research Unit (PSSRU) at the University of Kent.[38–40] Residential care costs were taken from national tariffs reported in *Unit Costs of Health and Social Care 2013*.[38] Similarly, community health and social care costs were obtained from *Unit Costs of Health and Social Care 2015*.[39] NHS medication prices (per milligram) were obtained from the *Prescription Cost Analysis – England, 2016* database[37] and equipment and adaptation costs from the NHS Supply Chain's *National Catalogue* (2014–15).[41] *Unit Costs of Health and Social Care 2016* was used to inflate or deflate costs when necessary to 2015–16 prices (GBP).[40] No discounting of costs was applied because cost-effectiveness for the purposes of the within-trial economic evaluation was determined over a 6-month time horizon.

Calculation of utilities and quality-adjusted life-years

The economic evaluation estimated QALY profiles for trial participants based on patient reports of preference-based HRQoL outcomes. The HRQoL of trial participants was assessed using the EQ-5D-3L,[42] measured at baseline, and at 3 and 6 months post ICU discharge as a secondary outcome in the trial. The EQ-5D-3L descriptive system consists of the following five dimensions: 'mobility', 'self-care', 'usual activities', 'pain/discomfort' and 'anxiety/depression'. Each dimension is divided into three ordinal levels coded: (1) no problems, (2) some or moderate problems and (3) severe or extreme problems.[43,44] For the purposes of this study, the UK time trade-off tariff was applied to each set of responses to generate an EQ-5D-3L utility score (preference weight) for each participant.[42] The utility scores generated through this method range from –0.59 to 1.0, with 1.0 representing full health, zero representing death and values below 0 indicating health states that are considered to be worse than death. The second measurement component of the EQ-5D-3L is the EuroQol visual analogue scale (EQ VAS), which records the respondent's self-reported health on the day of the survey on a 20-cm, vertical VAS; the scale ranges from 100 (best imaginable health state) to 0 (worst imaginable health state).[43] QALYs were calculated as the area under the curve, assuming a fixed baseline utility score of –0.402 (equivalent to an unconscious health state) and using linear interpolation between baseline and follow-up utility scores.[45]

The SF-12 was also completed at the same time point as the EQ-5D-3L and responses were converted into Short Form questionnaire-6 Dimensions (SF-6D) utilities based on the algorithm provided by Brazier *et al.*[46] For the SF-6D utility scores, the fixed baseline value was set to zero when constructing QALYs for the purpose of a sensitivity analysis. No discounting of QALYs was applied for the purposes of the within-trial economic evaluation because cost-effectiveness was determined over a 6-month time horizon. Participants surviving to hospital discharge were also asked to recollect their pre-admission (pre-randomisation) health state using both the EQ-5D-3L and the SF-12; utility scores generated by these HRQoL assessments were used to inform a separate sensitivity analysis.

Missing data

Multiple imputation (MI) using the Markov chain Monte Carlo method of chained equations was used for the base-case analysis to impute missing data. This avoids potential biases associated with complete-case analysis and is consistent with good practice guidance. MI was used at the aggregate level (i.e. on missing total costs or QALYs). When data are missing at random (MAR), MI provides unbiased estimates of treatment effect. The MAR assumption was explored in the data, using logistic regression for missingness of total costs and QALYs for each time point (separately) as a function of baseline variables. A model was used to generate multiple imputed data sets for treatment groups, in which missing values were estimated conditionally on available covariates: age, sex, centre, presence/absence of COPD, non-operative/operative and post-SBT $PaCO_2$, such that a complete data set was generated, reflecting the distributions and correlations between variables in the observed data. Mean matching using predictive methods was used to improve estimates of imputed values as normality could not be assumed. Each imputed data set was analysed independently using model-based approaches; estimates obtained were pooled to generate mean and variance estimates of costs and QALYs using Rubin's rule in order to capture within and between variances for imputed samples.[47] Information loss from finite imputation sampling was minimised using 20 data sets, resulting in minimal loss of efficiency (< 0.5%) when compared with infinite sampling. Imputed and observed values were compared in order to establish that imputation did not introduce bias into subsequent estimations.

Analyses of resource use, costs and outcome data

Resource use items were summarised by treatment group and assessment point; differences between groups were analysed using two sample *t*-tests for continuous variables. The mean [standard error (SE)] of each resource type, including by resource category, was estimated by trial allocation group for each time period. Costs were estimated from both a NHS and a PSS perspective and, for the purposes of a sensitivity analysis, from a broader societal perspective. Differences between groups in terms of costs, along with their CIs, were estimated and reported. Non-parametric bootstrap estimates using 10,000 replications[35] were also calculated for differences, along with their CIs. For each EQ-5D-3L dimension, the proportion of participants with suboptimal levels of function (some or moderate problems, or severe or extreme problems) at each assessment point was compared between treatment groups using chi-squared tests. EQ-5D-3L utility score differences between the groups at each follow-up point were tested using two-sample *t*-tests for unequal variance.

Model-based methods (seemingly unrelated regression) were used to estimate mean incremental changes in costs and QALYs and accounted for the correlation between costs and outcomes within the data while adjusting for covariates, including baseline costs (for the cost equation) and baseline utility scores (for the QALY equation) to adjust for potential baseline imbalances. Non-parametric bootstrap methods were used to generate the joint distributions of costs and outcomes to populate the cost-effectiveness plane. Bootstrapping (using the bias-corrected non-parametric approach) is a resampling method that jointly resamples costs and outcomes from the observed data while holding the sample correlation structure. From each bootstrap sample (of 10,000 samples), changes in costs and QALYs were estimated. Mean estimates are reported with 95% CIs.

Cost-effectiveness analyses

The incremental cost-effectiveness ratio (ICER) was estimated as the difference between the trial comparators in mean total costs divided by the difference in mean total QALYs. Value for money was determined by comparing the ICER value with a cost-effectiveness threshold value; the NICE cost-effectiveness threshold for British studies typically ranges between £20,000 and £30,000 per QALY. In addition, a £15,000 cost-effectiveness threshold

was used to reflect more recent trends in health-care decision-making.[48] This represents society's willingness to pay for an additional QALY; ICER values lower than the threshold could be considered to be cost-effective for use in the NHS. Base-case assumptions were explored using a range of supportive sensitivity analyses.

The incremental net monetary benefit (INMB) of using the NIV protocol was also reported as a recalculation of the ICER at a range of cost-effectiveness thresholds. The INMB succinctly describes the resource gain (or loss) when investing in a new intervention when resources can be used elsewhere at the same threshold. INMB estimates were used to generate cost-effectiveness acceptability curves (CEACs). A CEAC compares the likelihood that interventions are cost-effective as the cost-effectiveness threshold varies.

All statistical analyses and cost-effectiveness modelling were conducted in SAS® software version 9.4 (SAS Institute Inc., Cary, NC, USA) on a Microsoft Windows® (Microsoft Corporation, Redmond, WA, USA) platform.

Sensitivity and subgroup analyses

Several sensitivity analyses were undertaken to assess the impact on the base-case economic evaluation. The following sensitivity analyses were considered for the cost-effectiveness outcomes: (1) recalculation from a broader societal perspective (adopting a wider societal perspective that includes costs incurred by all sectors of the economy and by patients, families and informal carers), (2) complete-case analysis (i.e. those with complete cost and outcome data throughout the trial time horizon), (3) using the SF-6D utility scores estimated from the SF-12 for the purposes of QALY estimation and (4) additionally using the pre-randomisation EQ-5D-3L utility value (recalled at hospital discharge) as a covariate for the purpose of adjusting for QALY differences. Prespecified subgroup analyses were also conducted for the main cost-effectiveness results to explore heterogeneity in the trial population. These were conducted by (1) presence/absence of COPD and (2) operative status (non-operative vs. operative).

Long-term cost-effectiveness model

Modelling survival data

Long-term cost-effectiveness was determined over a 5-year time horizon by modelling and extrapolating survival time between randomisation and death, after examining the observed survival curves (*Figure 16a*). A flexible parametric model using cubic splines (Royston–Parmar approach) was used.[49] The approach adopted avoids the use of life tables to estimate projected survival rates. Extrapolation beyond 5 years is considered to be highly speculative and uncertain because most deaths occurred between randomisation and hospital discharge.

The fitted model (Royston–Parmar model) was used to predict the survival rates at each time point (*Figure 16b*). The survival rates at each 3-monthly interval (3, 6, 9, 12 . . . 60 months) were used to determine the expected costs and derive the QALYs (at an aggregate level).

Modelling health utilities between hospital discharge and death

Health utilities were extrapolated between 6 months post randomisation and death for each treatment group separately. The extrapolation was determined under the main assumption that utilities remained constant at 6 months post randomisation.

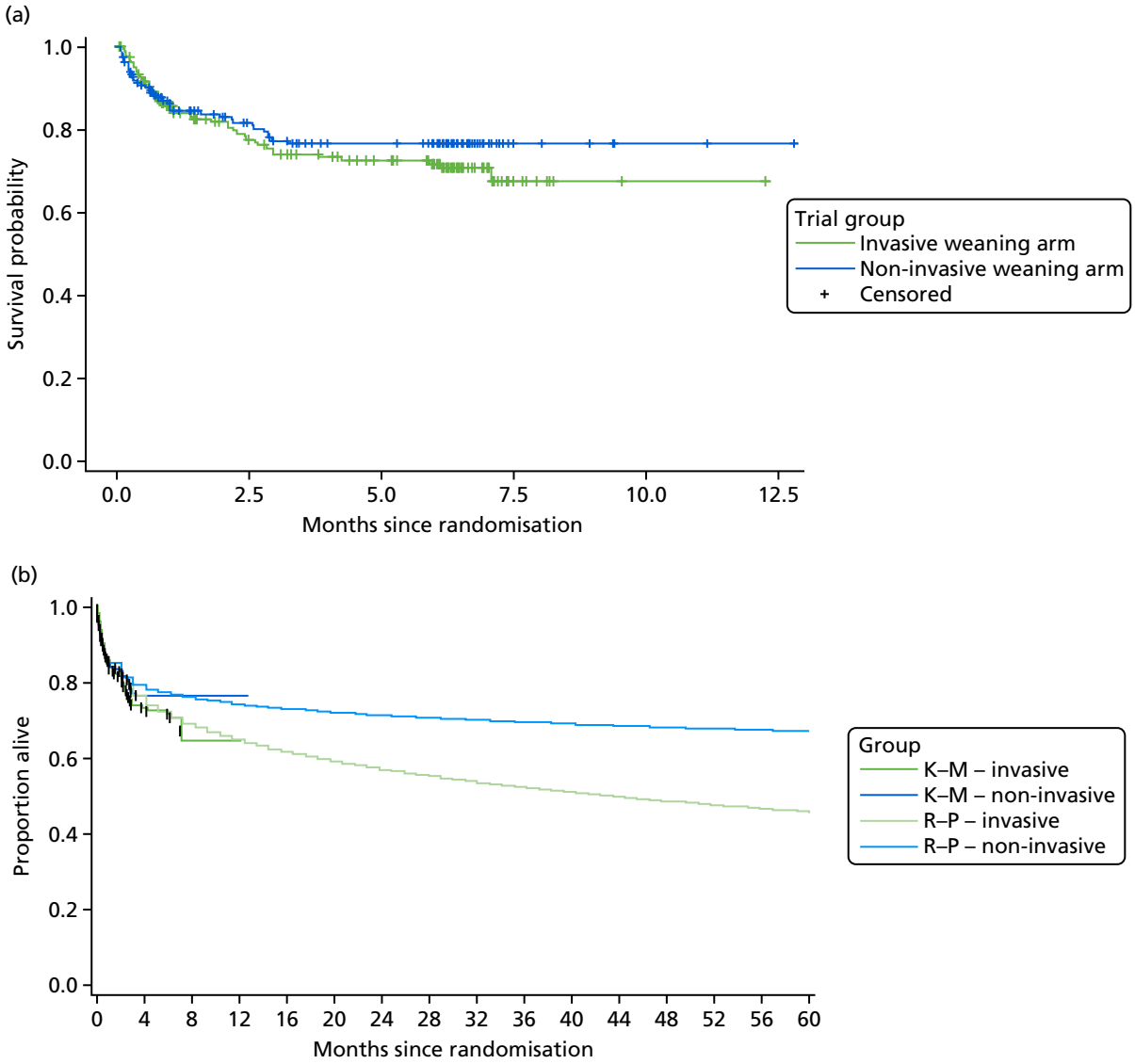


FIGURE 16 (a) Observed Kaplan–Meier survival; and (b) extrapolated and observed survival over 5 years. R–P, Royston–Parmar three-knot; K–M, Kaplan–Meier.

Adjusted health utilities and quality-adjusted life-years

The estimated health utilities at each time point between 6 months post randomisation and 60 months post randomisation were multiplied by the predicted proportion of participants alive at the corresponding time point. These values were then used to compute the 5-year QALY estimate for each group by computing the area under the curve using the linear trapezoidal rule after discounting at 3.5% per annum in each of years 2–5.

Modelling longer-term costs

Costs between 6 months post randomisation and death were estimated by using the observed 3- to 6-month post-randomisation total costs, adjusted for covariates (e.g. age, centre, COPD status), and multiplying by the predicted survival probabilities over the period extending to 5 years post randomisation (see *Table 33* in *Appendix 3*). The primary long-term cost-effectiveness analyses was considered under the assumption that the longer-term costs and benefits (health utilities) for the NIV group are equal to those for the IMV group and only the proportion of participants alive beyond 6 months adjusts these costs and benefits (see *Table 33* in *Appendix 3*).

Additional sensitivity analyses included:

1. assuming that, after 6 months post randomisation, costs and health utilities were the same between groups, but survival rates in the NIV group were 10% lower (justified by an examination of the plots of log-survival and hazard function) and similar to those of the IMV group
2. assuming that, after 6 months post randomisation, costs and health utilities are carried forward (unequal) from 3 to 6 months onwards until 5 years post randomisation
3. assuming that, after 6 months post randomisation, costs were the same between groups, but health utilities were carried forward from the last estimates observed.

In summary, for the long-term cost-effectiveness analyses, the analyses in *Table 34* (see *Appendix 3*) were applied.

Results

Trial population

A total of 364 participants were randomised into the Breathe trial: 182 to the 'non-invasive weaning' group and 182 to the 'invasive weaning' group. Complete health resource information was available for all 354 participants between randomisation and ICU discharge. Consequently, the base-case economic analyses include data from all 354 participants. Approximately 52% and 50% of all health resource use data were complete at 3 months for the NIV and IMV groups, respectively; this diminished to 51% and 46%, respectively, by 6 months (*Table 23*). A complete QALY profile was available for 182 out of 364 (50%) participants. For about 65% of participants (see *Table 35*, *Appendix 3*), a complete QALY profile was available after deaths were taken into account. Consequently, about 35% of QALY data and between 6% and 40% of costs (at the component level) were missing (and subsequently imputed) for the primary analysis.

TABLE 23 Summary of data completeness of economic measures

		Trial group, *n* (%)					
		Non-invasive weaning group (*N* = 182)			Invasive weaning group (*N* = 182)		
Resource use item	Time point	Completed[a]	Unavailable[b]	Missing[c]	Completed[a]	Unavailable[b]	Missing[c]
ICU admission length of stay by organ support and level of care	Initial hospitalisation	182 (100)	0 (0)	0 (0)	182 (100)	0 (0)	0 (0)
Post-ICU admission length of stay and procedures	Initial hospitalisation	182 (100)	0 (0)	0 (0)	182 (100)	0 (0)	0 (0)
Inpatient care (readmissions)	3 months	95 (52)	87 (48)	0 (0)	91 (50)	89 (49)	2 (1)
	6 months	93 (51)	88 (48)	1 (1)	84 (46)	97 (53)	1 (1)
Outpatient care (hospitals/clinics)	3 months	95 (52)	87 (48)	0 (0)	91 (50)	89 (49)	2 (1)
	6 months	93 (51)	88 (48)	1 (1)	84 (46)	97 (53)	1 (1)
Residential care services	3 months	95 (52)	87 (48)	0 (0)	91 (50)	89 (49)	2 (1)
	6 months	93 (51)	88 (48)	1 (1)	84 (46)	97 (53)	1 (1)
Community health and social care	3 months	95 (52)	87 (48)	0 (0)	91 (50)	89 (49)	2 (1)
	6 months	93 (51)	88 (48)	1 (1)	84 (46)	97 (53)	1 (1)

TABLE 23 Summary of data completeness of economic measures (*continued*)

		Trial group, *n* (%)					
		Non-invasive weaning group (*N* = 182)			Invasive weaning group (*N* = 182)		
Resource use item	Time point	Completed[a]	Unavailable[b]	Missing[c]	Completed[a]	Unavailable[b]	Missing[c]
Medications	3 months	95 (52)	87 (48)	0 (0)	91 (50)	89 (49)	2 (1)
	6 months	93 (51)	88 (48)	1 (1)	84 (46)	97 (53)	1 (1)
Equipment or aids	3 months	95 (52)	87 (48)	0 (0)	91 (50)	89 (49)	2 (1)
	6 months	93 (51)	88 (48)	1 (1)	84 (46)	97 (53)	1 (1)
Broader societal resource use	3 months	95 (52)	87 (48)	0 (0)	91 (50)	89 (49)	2 (1)
	6 months	93 (51)	88 (48)	1 (1)	84 (46)	97 (53)	1 (1)
EQ-5D-3L index	Prior to hospital admission[d]	121 (66)	58 (32)	3 (2)	120 (66)	62 (34)	0 (0)
	3 months	91 (50)	87 (48)	4 (2)	88 (48)	91 (50)	3 (2)
	6 months	90 (49)	89 (49)	3 (2)	80 (44)	99 (54)	3 (2)
EQ VAS	Prior to hospital admission	121 (66)	58 (32)	3 (2)	120 (66)	62 (34)	0 (0)
	3 months	91 (50)	87 (48)	4 (2)	88 (48)	91 (50)	3 (2)
	6 months	91 (50)	90 (49)	3 (2)	82 (45)	101 (55)	3 (2)
SF-12	Prior to hospital admission	120 (66)	59 (32)	3 (2)	120 (66)	62 (34)	0 (0)
	3 months	91 (50)	87 (48)	4 (2)	88 (48)	91 (50)	3 (2)
	6 months	91 (50)	90 (49)	3 (2)	82 (45)	101 (55)	3 (2)

a Assessments were made; data available.
b Assessments not made; data collection forms missing (because of deaths, withdrawals from study or losses to follow-up).
c Assessments made, but data collection forms returned with incomplete data.
d These data were recollected using questionnaires administered at the point of discharge following the initial hospitalisation.

Resource use and costs

Direct resource and cost implications of the intervention

Table 35 (see *Appendix 3*) summarises resource use values by trial allocation, resource category and trial period for complete cases. *Table 36* (see *Appendix 3*) summarises the unit cost values applied to each resource input, whereas *Table 24* summarises the economic cost values by trial allocation, resource category and trial period. The resource and cost components associated with the intervention are aggregated into five groups: (1) intensive care support, which includes organ support, level of care and use of sedatives; (2) tracheostomy; (3) use of high-cost antiviral and antifungal or other high-cost drugs in the ICU; (4) hospital care between ICU discharge and hospital discharge; and (5) use of any emergency transport to transfer patients between hospital sites. Total intervention costs are also presented by treatment group. These varied between £2862 and £172,543 for the non-invasive weaning group and between £5146 and £195,855 for the invasive weaning group.

There were no statistical differences in the mean costs between randomisation and initial hospital discharge, which were £29,697 and £32,052 for the non-invasive weaning and invasive weaning groups, respectively (mean cost difference –£2355, 95% CI –£7292 to £2750; $p = 0.4472$). There were no statistical differences in any of the component costs related to ICU stay (see *Table 24*), although, on average, the mean costs were lower for the non-invasive group for most cost components.

Broader resource use

Table 35 (see *Appendix 3*) also shows resource use values for participants with complete data by trial group allocation, resource use category and trial period. The resource values are presented for subcategories of resource use, including hospital inpatient and outpatient care, residential care, community health and social care, medications, and equipment and aids. Broader societal resource input and costs included travel, child care, income lost, housework help and laundry services costs.

In terms of specific health resource use for non-invasive weaning versus invasive weaning at 3 months, notable differences were observed for residential rehabilitation use (0.7 vs. 1.6 days; $p = 0.296$), home help/care work support (6.8 vs. 3.9 visits; $p = 0.1868$) and occupational therapist visits (0.8 vs. 0.4 visits; $p = 0.3318$); in addition, a smaller proportion of non-invasive weaning group participants were supported through equipment and aids (56% vs. 65%; $p = 0.2113$). Between 3 and 6 months, 10% fewer participants were admitted for an inpatient stay, such that the average length of stay was lower with non-invasive weaning (3.1 vs. 4.3 days); similarly, 20% fewer participants had outpatient clinic visits (53% vs. 73%; $p = 0.00634$). However, between randomisation and 6 months post discharge, the mean length of stay during hospital readmissions was higher for the non-invasive weaning group than for the invasive weaning group (9.5 vs. 5.2 days; $p = 0.0604$), suggesting the potential for later longer-term costs associated with survivors of non-invasive weaning. This feature is also noted for other health resource items in *Table 35* (see *Appendix 3*): rehabilitation days (3.1 vs. 0.6 days; $p = 0.1262$); general practitioner (GP) home visits (0.8 vs. 0.4 visits; $p = 0.5768$); district nurse visits (8.4 vs. 6.6 visits; $p = 0.4588$); and purchase of aids and equipment (26% vs. 12%; $p = 0.01878$). For all other resource use items, there were no noticeable differences between the trial groups.

Economic costs

Economic costs for participants with complete data are presented in *Table 24* by trial group, trial period and cost category. Based on complete cost data, non-invasive weaning was, on average, less costly. The total mean cost for the non-invasive weaning group was lower from a NHS/PSS perspective (£31,711 vs. £32,468), although this difference was not statistically significant (bootstrap 95% CI –£6642 to £5246; $p = 0.8321$). This was also true when costs were considered from a broader societal perspective: £31,934 versus £32,999 (bootstrap 95% CI –£6804 to £5056; $p = 0.7981$).

Between randomisation and 6 months, initial hospitalisation costs were lower (see *Table 24*) for the non-invasive weaning group (£28,842 vs. £30,719; $p = 0.593$). Similarly, residential care costs and equipment and aids costs were higher, on average, for the non-invasive weaning group than for the invasive weaning group (residential care costs £405 vs. £42; $p = 0.0180$; equipment and aid costs £59 vs. £29; $p = 0.0276$). Moreover, the total post-initial-hospitalisation health and social care burden (in terms of costs) from the NHS/PSS perspective was higher (see *Table 24*) for the non-invasive weaning group than for the invasive weaning group (£2869 vs. £1749; $p = 0.0494$). Mean total broader societal costs were lower over the 6 months for the non-invasive weaning group than for the invasive weaning group (£223 vs. £532; $p = 0.0142$). There were also statistically significant differences between the groups in terms of broader societal costs at 3 months: £138 in the non-invasive weaning group versus £456 in the invasive weaning group ($p = 0.0012$).

Health-related quality-of-life outcomes

There were no statistically significant differences in suboptimal levels of function in HRQoL for participant-reported dimensions of the EQ-5D-3L between the intervention and control groups prior to hospital admission or at 3 months post ICU discharge (see *Table 37* in *Appendix 3*). However, the mean EQ-5D-3L utility score among complete cases was statistically significantly lower (see *Table 37* in *Appendix 3*) at 6 months post randomisation in the non-invasive weaning group (0.53 vs. 0.66; $p = 0.0147$). In contrast, the mean QALY value, which takes into account utility scores across multiple time points and sets a utility score of zero from the date of death onwards, was, on average, higher for the non-invasive weaning group than for the invasive weaning group (0.0928 vs. 0.0747; $p = 0.4522$), although the mean QALY difference was not statistically significant (*Table 25*). There were no (statistically significant) differences in the EQ VAS scores between the intervention and control groups at each of the time points of assessment.

TABLE 24 Economic costs for complete cases by trial allocation, trial period and cost category (GBP, 2015–16 prices)

Resource use category by time period	Trial group, mean (SE)		Mean difference	*p*-value	Bootstrap 95% CI
	Non-invasive	Invasive			
Randomisation to hospital discharge	**n = *182***	**n = *182***			
Intensive care support[a]	20,509.7 (1762.56)	22,018.9 (1685.17)	–1509.2	0.5515	(–5533.9 to 2586.3)
Tracheostomy	980.9 (131.08)	1254.6 (141.7)	–273.7	0.1570	(–584.1 to 57.2)
Antivirals/antifungals	455.7 (194.91)	758.2 (219.66)	–302.5	0.3036	(–768.1 to 215.8)
Hospital care between ICU and hospital discharge	7694.5 (695.69)	7967.0 (1038.27)	–272.5	0.8275	(–2511.2 to 1682.5)
Transfer by ambulance/NHS transport	56.0 (7.97)	53.1 (7.82)	2.87	0.7971	(–16.1 to 20.7)
Total NHS and PSS costs	29,696.8 (2069.8)	32,051.8 (2204.56)	–2355.0	0.4472	(–7291.5 to 2750.0)
Hospital discharge to 3 months post randomisation	**n = *130***	**n = *131***			
Health and social care resource use					
Hospital inpatient care	686.8 (163.83)	381.8 (123.63)	305.0	0.1387	(–30.0 to 642.2)
Hospital outpatient care	130.7 (25.95)	86.7 (17.41)	–4.0	0.1602	(–5.2 to 97.3)
Residential care	158.6 (55.55)	43.2 (22.64)	115.4	0.0560	(20.1 to 219.7)
Community health and social care	280.7 (46.03)	301.3 (75.31)	–20.6	0.8157	(–171.3 to 114.3)
Medications	67.8 (21.23)	139.5 (36.84)	–71.7	0.0935	(–141.4 to -4.7)
Equipment and aids	32.2 (8.79)	13.9 (4.71)	18.3	0.0679	(2.8 to 35.5)
Total NHS and PSS costs	1356.8 (196.32)	966.4 (151.99)	390.4	0.0836	(–47.1 to 775.7)
Broader societal costs					
Additional[b]	108.6 (33.02)	297.7 (129.15)	–189.1	0.0926	(–324.6 to –4.2)
Equipment and aids (private and charity)	29.3 (10.53)	158.3 (120.1)	–129	0.2854	(–259.3 to 131.4)
Total broader societal costs	137.9 (22.47)	456.0 (93.68)	–318.1	0.0012	(–434.1 to –158.4)
Total societal costs	1494.7 (179.61)	1422.4 (202.29)	72.3	0.3869	(–219.2 to 676.5)
3 months post randomisation to 6 months post randomisation	**n = *129***	**n = *127***			
Health and social care resource use					
Hospital inpatient care	788.4 (203.12)	403.0 (144.18)	385.4	0.1233	(–7.0 to 1101.3)
Hospital outpatient care	131.5 (20.23)	123.0 (24.85)	28.50	0.7913	(–56.8 to 105.0)
Residential care	264.4 (140.96)	0.0 (0.00)	264.0	0.0630	(57.6 to 515.2)
Community health and social care	373.2 (102.74)	214.5 (66.54)	158.7	0.1963	(–33.2 to 362.5)
Medications	176.2 (45.39)	206.0 (46.65)	–29.8	0.6480	(–135.9 to 78.5)
Equipment and aids	30.9 (6.30)	17.4 (5.25)	–13.5	0.1010	(–0.27 to 26.9)
Total NHS and PSS costs	1764.6 (258.47)	963.9 (157.71)	798.6	0.0031	(308.9 to 1294.7)

continued

TABLE 24 Economic costs for complete cases by trial allocation, trial period and cost category (GBP, 2015–16 prices) (*continued*)

Resource use category by time period	Trial group, mean (SE)		Mean difference	*p*-value	Bootstrap 95% CI
	Non-invasive	Invasive			
Broader societal costs					
Additional[b]	171.8 (70.17)	245.9 (110.38)	–74.1	0.3864	(–207.6 to 52.9)
Equipment and aids (private and charity)	25.9 (9.67)	14.7 (12.5)	11.2	0.4788	(–10.8 to 33.2)
Total broader societal costs	197.7 (45.3)	260.6 (66.3)	–62.9	0.4336	(–173.9 to 48.1)
Total societal costs	1962.3 (265.94)	1224.5 (178.96)	737.8	0.2262	(–432.6 to 1928.3)
From randomisation to 6 months post randomisation	**n = *129***	**n = *127***			
Initial hospitalisation costs					
Intensive care support[a]	20,815.7 (2134.03)	21,659.9 (2059.30)	–844.2	0.7761	(–5699 to 4114)
Tracheostomy	922.6 (149.01)	1129.5 (159.01)	–206.9	0.3435	(–570.1 to 151.2)
Antivirals/antifungals	448.2 (234.98)	968.8 (288.76)	–520.6	0.1635	(–1131.2 to 89.9)
Hospital care between ICU and hospital discharge	6613.3 (707.09)	6914.7 (896.01)	–301.4	0.7921	(–2229 to 1519)
Transfer by ambulance/NHS transport	42.6 (8.33)	46.1 (8.57)	–3.5	0.7681	(–23.3 to 16.1)
Total NHS and PSS costs	28,842.4 (2462.57)	30,719.0 (2501.67)	–1876.6	0.5934	(–7612 to 3989)
Post-initial-hospitalisation costs					
Health and social care resource use					
Hospital inpatient care	1323.6 (294.88)	698.2 (221.55)	625.4	0.0913	(28.3 to 1236.9)
Hospital outpatient care	240.7 (39.10)	188.8 (34.85)	51.9	0.3222	(–33.4 to 139.6)
Residential care	405.4 (150.44)	41.6 (21.81)	363.8	0.0180	(132.7 to 632.6)
Community health and social care	613.8 (129.40)	475.5 (124.74)	138.3	0.4426	(–153.7 to 424.5)
Medications	226.3 (59.99)	315.8 (68.56)	–89.5	0.3268	(–237.9 to 60.7)
Equipment and aids	59.1 (10.89)	28.6 (8.45)	30.5	0.0276	(7.3 to 53.4)
Total NHS and PSS costs	2868.9 (392.94)	1748.5 (276.45)	1120.4	0.0494	(176.5 to 1542.9)
Broader societal costs					
Additional[b]	171.7 (67.65)	374.6 (164.09)	–202.9	0.2542	(–441.1 to –23.3)
Equipment and aids (private and charity)	51.2 (24.45)	157.0 (98.87)	–105.8	0.2498	(–179.3 to 16.0)
Total broader societal costs	222.9 (97.44)	531.6 (120.33)	–309.7	0.0142	(–489.5 to 272.6)
Total societal costs	3091.8 (392.94)	2280.1 (276.45)	811.7	0.3163	(–128.3 to 1371.6)
Total NHS/PSS including ICU	31,711.3 (2498.47)	32,467.5 (2550.99)	–756.2	0.8321	(–6642.1 to 5245.7)
Total societal including ICU	31,934.2 (2498.58)	32,999.1 (2547.95)	–1064.9	0.7981	(–6804.2 to 5055.9)

a Costs based on the number of organs supported daily during the critical care period.
b This includes costs of travel, child care, housework help and laundry services, as well as income lost.

TABLE 25 Patient-reported EQ-5D-3L QALYs (complete cases, baseline fixed)

	QALY (EQ-5D-3L participant)[a]	
Parameter	*n*	Mean
Non-invasive (SE)	120	0.0928 (0.0616)
Invasive (SE)	118	0.0747 (0.0179)
Mean difference[b]	–	0.0181
p-value (95% CI)	–	0.4522 (–0.0293 to 0.0656)

a Estimated QALYs are determined using fixed baseline and also setting utilities to zero from the date of death for participants who died.
b Comparisons of EQ-5D-3L QALYs using student's *t*-test for unequal variances assuming a fixed baseline of –0.402.

Cost-effectiveness results

Base-case analysis

The incremental cost-effectiveness of non-invasive weaning is shown in *Table 26* for the participants with costs and health outcomes data subject to MI. When a NHS/PSS perspective was adopted (i.e. that which was adopted for the baseline analysis) and health outcomes were measured in terms of QALYs, the mean total cost was £36,313 in the NIV group, compared with £36,615 in the IMV group, generating a mean incremental cost of –£302. The NIV intervention was also associated with a non-statistically significant increase in QALYs (0.02 QALYs, 95% CI –0.01 to 0.05) over the entire 6-month follow-up period. In health economic terms, the intervention was dominant as average costs were lower and the net effect was higher.

Incremental net monetary benefit

The associated mean INMB of non-invasive weaning at cost-effectiveness thresholds of £15,000, £20,000 and £30,000 per QALY was £541, £620 and £779, respectively (see *Table 25*). The base-case mean INMB was > £0, suggesting that adopting the NIV protocol would result in a net economic gain of £620, on average, from a NHS/PSS perspective (INMB £541, 95% CI –£4545 to £5928), assuming a cost-effectiveness threshold of £20,000 per QALY. The cost-effectiveness plane (*Figure 17*) shows that the ICERs are largely spread across the north-east and south-east quadrants. These result in a probability of cost-effectiveness of between 57% and 59% (*Figure 18*); that is, if decision-makers are willing to pay between £15,000 and £30,000 for an additional QALY, the probability that the non-invasive weaning intervention is cost-effective falls just below 60% (see *Table 25*).

Sensitivity analyses

Several sensitivity analyses were undertaken to assess the impact of uncertainty surrounding key parameters or methodological features on the cost-effectiveness results. The probability that the non-invasive weaning intervention is cost-effective remained relatively static (at about 60%) for the majority of the sensitivity analyses (i.e. complete cases, societal costs, SF-6D-converted QALYs and using the recalled pre-randomisation EQ-5D-3L utility score as an additional covariate). All sensitivity analyses show that the average INMB is always > £0. However, because of high variability, the (bootstrap) 95% CIs cross zero and a conclusion of no difference between non-invasive weaning and invasive weaning in terms of the mean INMB cannot be completely (statistically) ruled out (see *Table 26* and *Figures 19–21*).

Subgroup analyses

Four subgroups were subjected to cost-effectiveness analyses to explore the heterogeneity in cost-effectiveness results: COPD (presence/absence) and operative status (operative/non-operative). All subgroup analyses were based on the patient-reported EQ-5D-3L and MI and covariate adjustments. COPD presence had a notable impact on the INMB values, with mean INMB values ranging between £7076 and £8829, depending on the value of the cost-effectiveness threshold. The probability of cost-effectiveness increased to a range of 82–87%

TABLE 26 Cost-effectiveness, cost per QALY (GBP, 2016): non-invasive vs. invasive weaning

Scenario	Probability of cost-effectiveness						INMB		
	Incremental cost (95% CI)	Incremental QALYs (95% CI)	ICER[a]	*p*-value[b]	*p*-value[c]	*p*-value[d]	INMB[b]	INMB[c]	INMB[d]
Base case (NHS/PSS perspective)									
Imputed attributable costs and QALYs (fixed baseline), adjusted for covariates	–302 (–5489 to 4761)	0.01589 (–0.01262 to 0.0465)	NIV dominant	0.57	0.58	0.59	541 (–4598 to 5833)	620 (–4545 to 5928)	779 (–4470 to 6162)
Sensitivity analyses									
1. Imputed societal attributable costs and QALYs (fixed baseline), adjusted for covariates	–339 (–5422 to 4645)	0.01631 (–0.01271 to 0.04714)	NIV dominant	0.57	0.58	0.60	584 (–4509 to 5733)	665 (–4473 to 5862)	828 (–4369 to 6075)
2. Complete cases (NHS/PSS) attributable costs and QALYs (fixed baseline), adjusted for covariates	–739.5 (–7139 to 5641)	0.01605 (–0.0211 to 0.0557)	NIV dominant	0.59	0.60	0.62	980 (–5539 to 7442)	1060 (–5505 to 7559)	1220 (–5456 to 7833)
3. Imputed attributable costs and QALYs (fixed baseline using SF-6D utility score), covariates adjusted	–330 (–540 to 4692)	0.0295 (–0.1367 to 0.1762)	NIV dominant	0.58	0.60	0.62	774 (–5033 to 6521)	922 (–5357 to 7025)	1218 (–6163 to 8267)
4. Imputed attributable costs and QALYs (fixed baseline), adjusted for covariates and pre-admission EQ-5D-3L covariate	–445 (–5305 to 4486)	0.0156 (–0.0151 to 0.0479)	NIV dominant	0.59	0.60	0.61	625 (–4809 to 5114)	735 (–4914 to 5044)	894 (–5182 to 4962)
Subgroup analyses (COPD and operative status)									
COPD: presence of COPD – imputed attributable costs and QALYs (fixed baseline), covariates adjusted EQ-5D-3L utility score	–5322 (–17,899 to 6431)	0.1169 (0.0353 to 0.215)	NIV dominant	0.82	0.84	0.87	7076 (–4817 to 19,814)	7660 (–4308 to 20,451)	8829 (–3368 to 21,731)
COPD: absence of COPD – imputed attributable costs and QALYs (fixed baseline), covariates adjusted EQ-5D-3L utility score	756 (–4768 to 6380)	–0.0050 (–0.0352 to 0.0258)	NIV dominated	0.40	0.40	0.39	–831 (–6588 to 4793)	–856 (–6629 to 4801)	–906 (–6745 to 4863)
Operative status: non-operative – imputed attributable costs and QALYs (fixed baseline), covariates adjusted EQ-5D-3L utility score	–1915 (–7955 to 3932)	0.03743 (0.00105 to 0.0766)	NIV dominant	0.75	0.76	0.79	2477 (–3491 to 8559)	2664 (–3394 to 8806)	3038 (–3134 to 9264)
Operative status: operative – imputed attributable costs and QALYs (fixed baseline), covariates adjusted EQ-5D-3L utility score	3266 (–6808 to 13,041)	–0.0311 (–0.0747 to 0.0135)	NIV dominated	0.27	0.26	0.25	–3733 (–13,560 to 6415)	–3888 (–13,736 to 6284)	–4200 (–14,063 to 6042)

a CIs based on 10,000 simulations. Each simulation based on model based means adjusted sex, age, COPD status, operative status, SBT $PaCO_2$ (post-SBT $PaCO_2$), unless stated otherwise (35% of missing data were imputed for QALYS and between 6% and 40% of costs were imputed depending on the cost component).
b Probability cost-effective or net monetary benefit if cost-effectiveness threshold is £15,000/QALY.
c Probability cost-effective or net monetary benefit if cost-effectiveness threshold is £20,000/QALY.
d Probability cost-effective or net monetary benefit if cost-effectiveness threshold is £30,000/QALY.

Note
ICER dominant indicates average costs were lower and average benefit greater for the non-invasive treatment group.

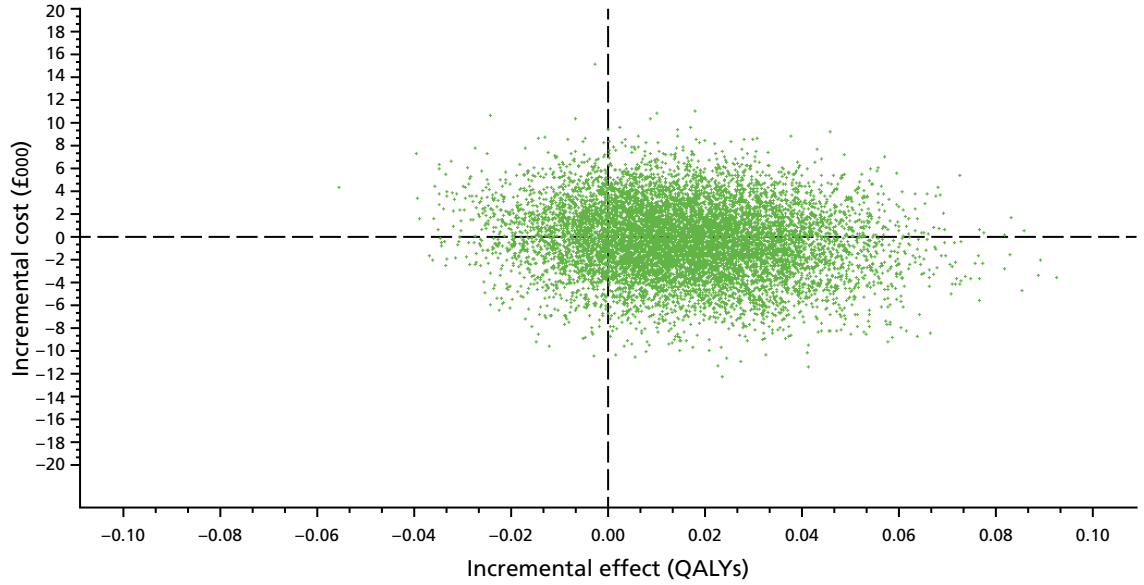


FIGURE 17 Cost-effectiveness plane for base case: fixed utility baseline, imputed costs, adjustment for covariates.

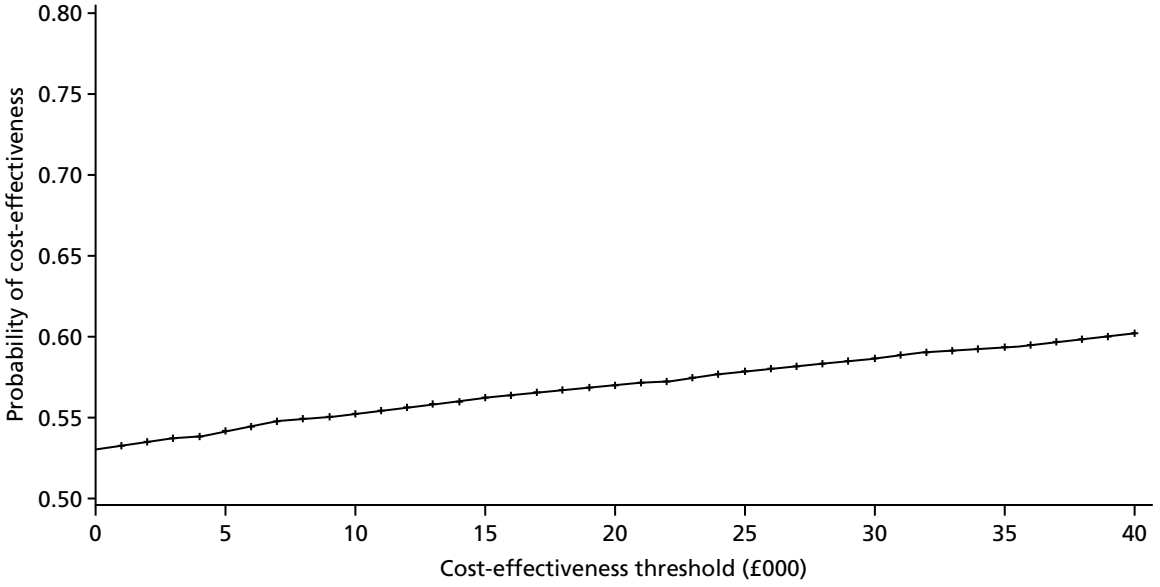


FIGURE 18 Cost-effectiveness acceptability curves for base case: fixed utility, imputed costs, adjustment for covariates.

depending on the value of the cost-effectiveness threshold in participants with COPD. Conversely, for participants with an absence of COPD, non-invasive weaning was less cost-effective than invasive weaning (see *Figures 19* and *21* and *Table 26*), resulting in non-invasive weaning being dominated by invasive weaning in health economic terms (as it was, on average, more costly and less effective). Similarly, for operative status, non-invasive weaning was dominated by invasive weaning and was therefore less cost-effective for this subgroup: non-invasive weaning was more costly and less effective, on average, and the mean INMB was negative, ranging between –£3733 and –£4200, with probabilities of cost-effectiveness ranging between 25% and 27%, depending on the value of the cost-effectiveness threshold.

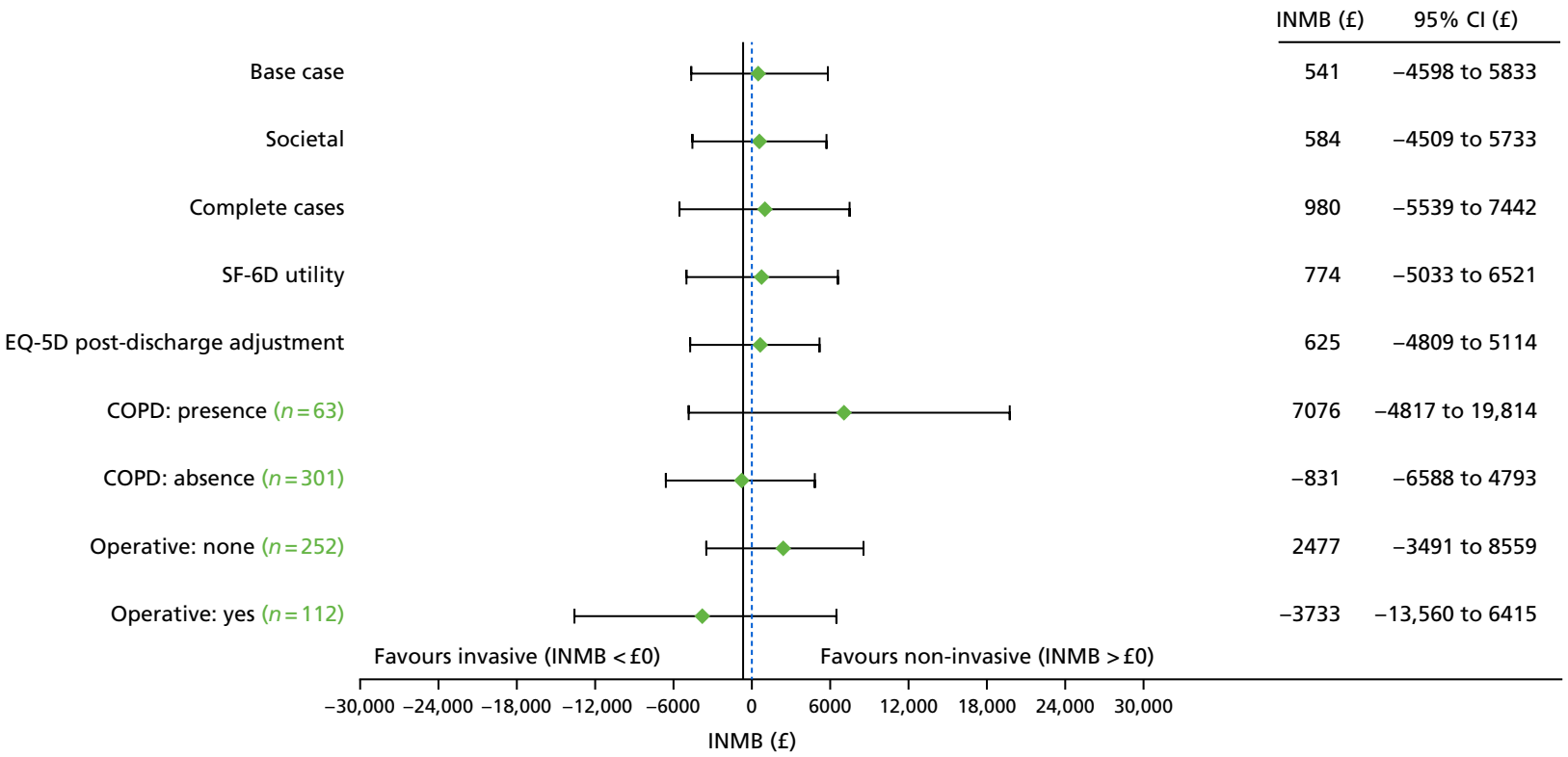


FIGURE 19 Sensitivity analyses and subgroup results (cost-effectiveness threshold of £15,000/QALY).

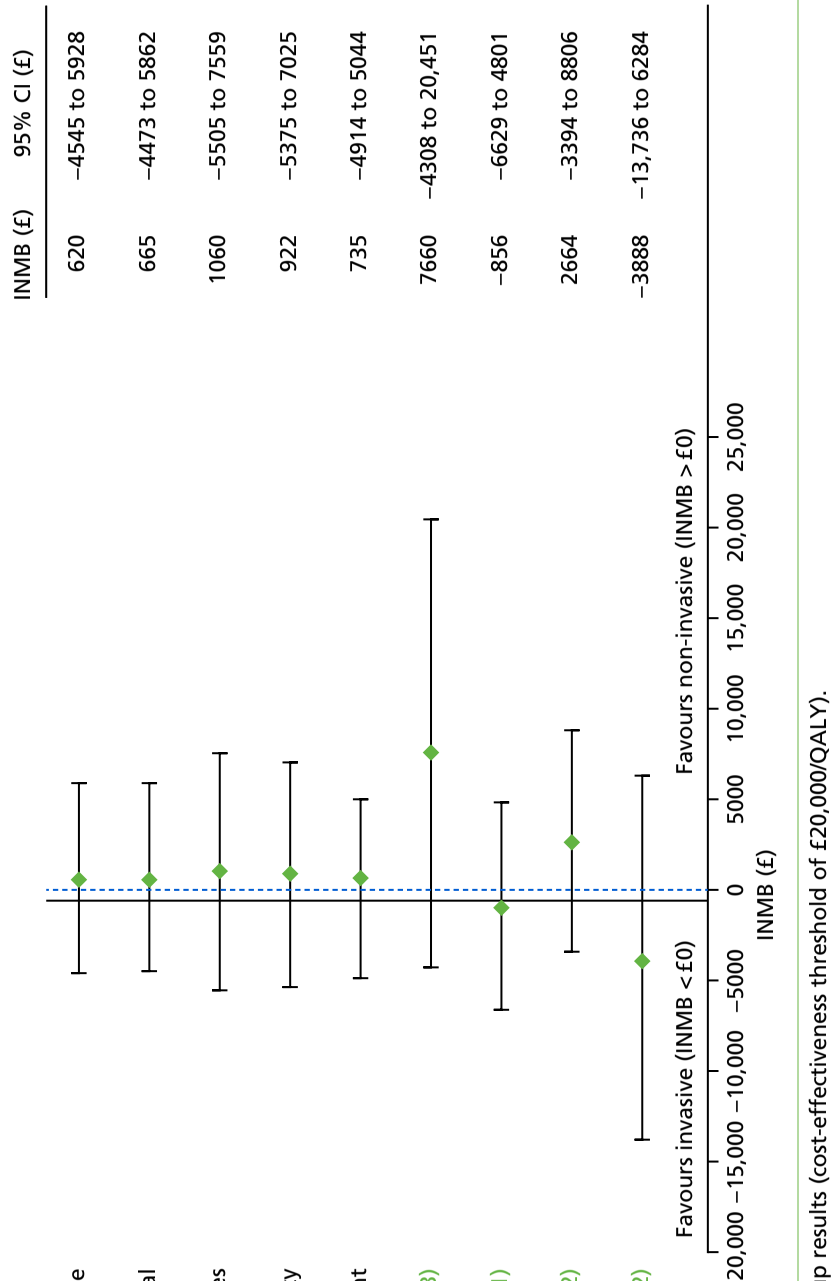


FIGURE 20 Sensitivity analyses and subgroup results (cost-effectiveness threshold of £20,000/QALY).

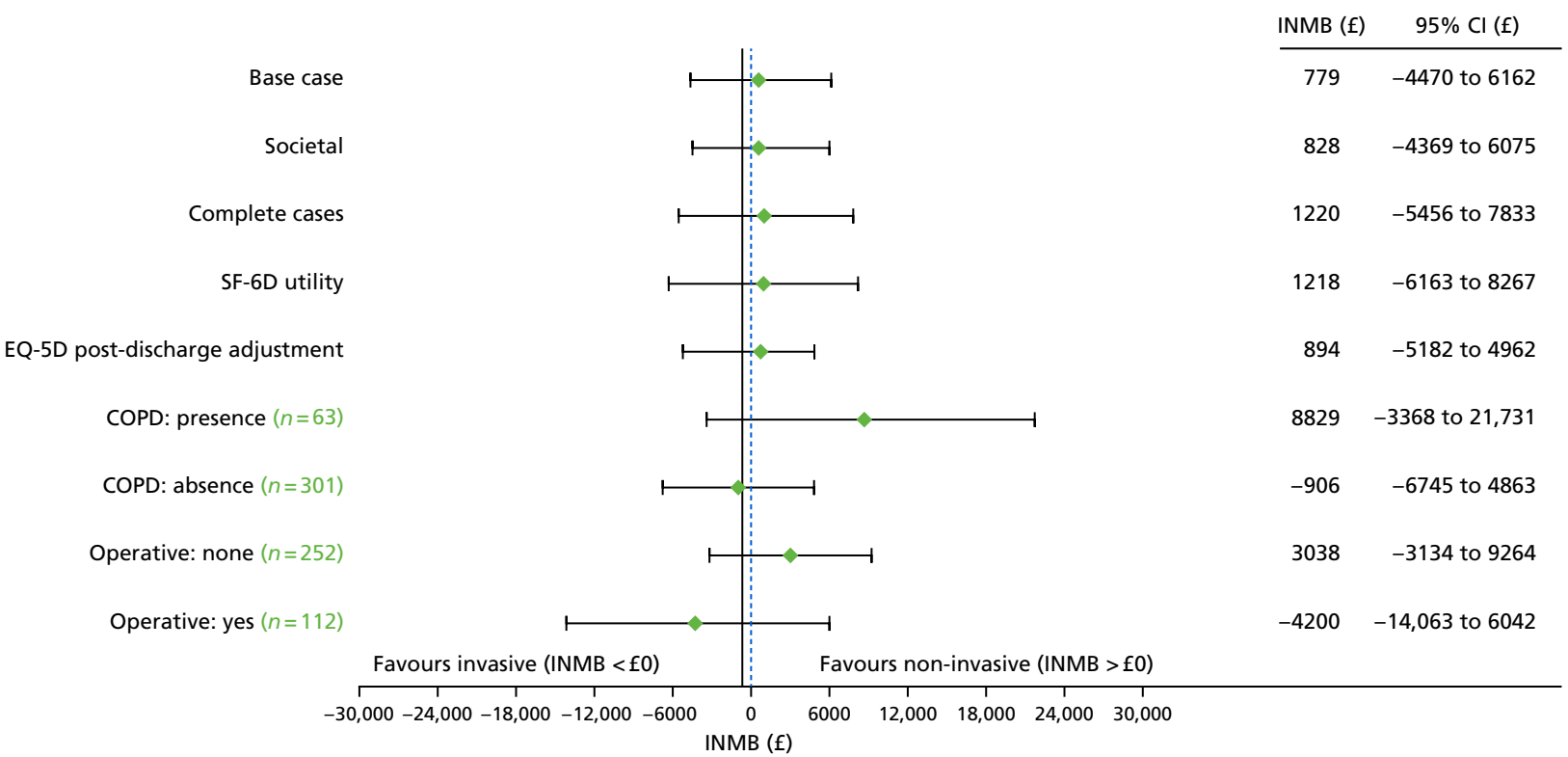


FIGURE 21 Sensitivity analyses and subgroup results (cost-effectiveness threshold of £30,000/QALY).

Results of the longer-term cost-effectiveness model

Survival rates

After fitting a Royston–Parmar[49] three-knot model (the best model based on lowest Akaike information criterion) using published SAS macros,[50] using a 5-year time horizon yielded a mean survival time of about 41.9 months versus 33.3 months for NIV versus IMV, respectively. The mean observed survival for NIV versus IMV was 4.12 months versus 4.07 months (*Table 27*) based on the observed Kaplan–Meier estimates from the within-trial data. By 5 years (60 months) post randomisation, 67% of participants were expected to remain alive in the NIV group, compared with 45% in the IMV group [see *Figure 16b* and *Table 33* (see *Appendix 3*)]. These survival rates are lower than the national average, as reported in mortality statistics of the general population with a similar age distribution to this population. This would be 95% at 5 years from a mean age of 63 years,[51] which, logically, are higher than the rates observed here as the participants in the study are patients from an ICU.

Both plots (*Figure 22*) of the log-survival (a) and the hazard (b) functions suggest that NIV has a trend of decreasing hazards (lower risk of death over time) whereas IMV appears to have an increasing hazard trend (higher risk of death over time). This is mainly as a result of the spike in hazards after month 6 because of a later death event in the IMV group. Both hazard functions suggest that risk of death is decreasing in a

TABLE 27 Longer-term costs and effects (base case)

Outcome	Trial group		Difference (NIV vs. IMV)
	NIV	IMV	
Survival			
Time horizon (months)	60	60	–
Mean observed survival (Kaplan–Meier) (months)	4.12	4.07	0.05
Royston–Parmar three-knot model, extrapolated survival[a] (mean) (months)	41.9	33.3	8.6
Utilities			
Constant (mean)[a]	0.444	0.361	0.083 (more effective)
QALYs			
QALY (discounted)[b]	2.247	1.824	0.427 (more effective)
Costs			
NHS/PSS during trial[c]	£31,711	£32,476	£765 (less costly)
> 6 months to 5 years[d]	£12,048	£9311	£2737 (more costly)
Total over 5 years, including ICU	£43,759	£41,787	£1972 (more costly)
ICER	–	–	£4618
INMB			
Cost-effectiveness threshold of £20,000	–	–	£6568
Cost-effectiveness threshold of £30,000	–	–	£10,838

a Mean utilities calculated as means across all observed and predicted estimates between randomisation and 5 years; this assumes utilities remain constant after 6 months post randomisation (i.e. carried forward).
b From baseline to 5 years as the area under the curve, when utilities are carried forward.
c Observed costs during the trial, including ICU costs (see *Table 24*).
d Extrapolated using predicted survival rates assuming equal future health resource use.

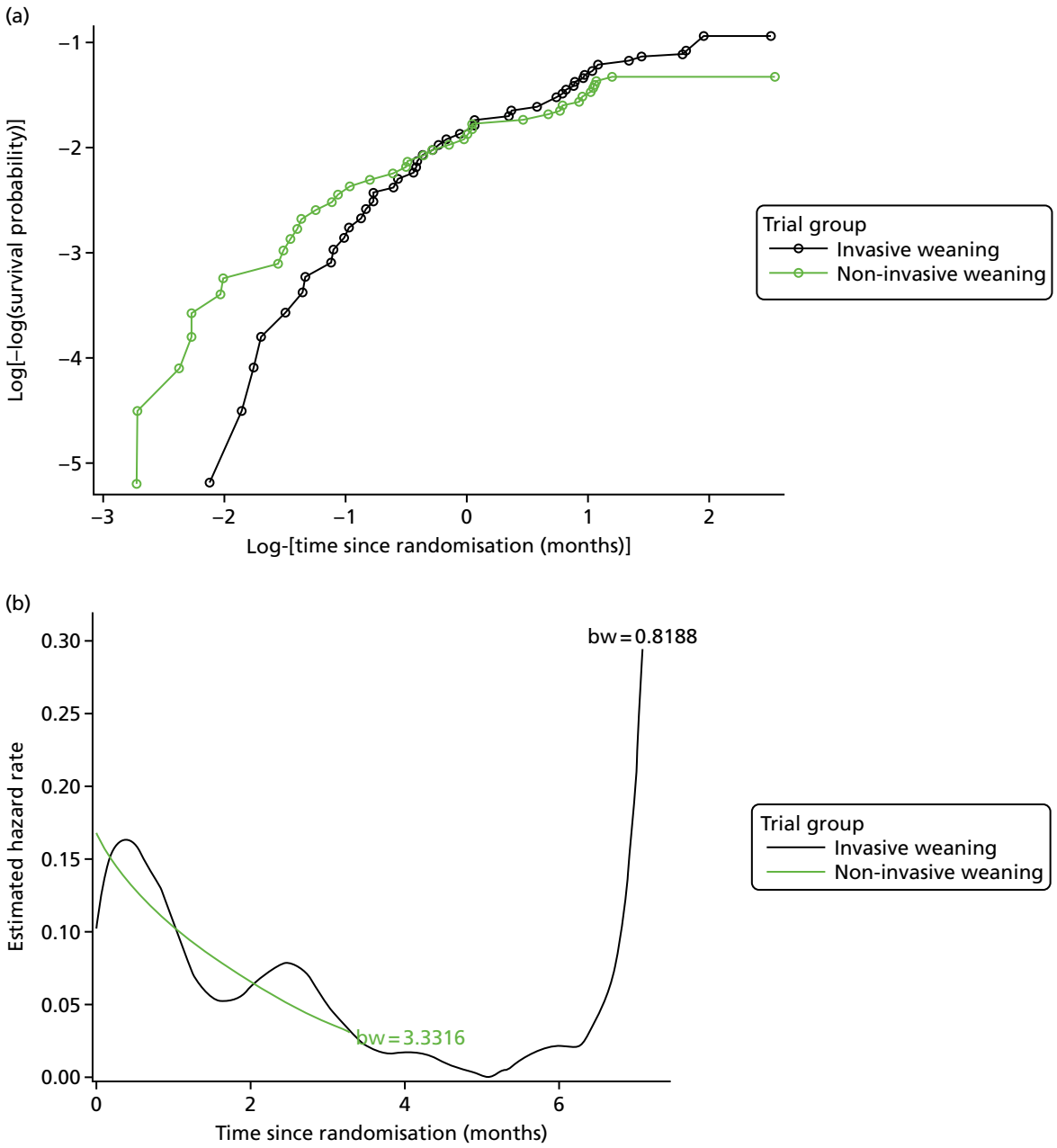


FIGURE 22 (a) Log-survival function; and (b) hazard function. bw, bandwidth.

similar trend until around 4 months post intervention, albeit with a more erratic hazard for the IMV group. After about 4 months, patients may die at a slightly faster rate (ignoring the spike) in the IMV group. Owing to a lack of further follow-up data, future death patterns may or may not be similar, although the curve trajectory for NIV suggests that the hazard curve may lie slightly above that of the IMV group. These plots partially support the extrapolated survival curves, suggesting that NIV patient death rates occur more slowly than death rates in the IMV group, but that survival rates over time may converge. On the basis of these results, an assumption of future costs and health utilities being similar between groups is not unreasonable.

Health utilities and quality-adjusted life-years

The mean health utility scores, calculated as means across all observed and predicted estimates between randomisation and 5 years, were estimated to be 0.444 versus 0.361 (NIV vs. IMV) assuming that utilities remained constant beyond 6 months (base case for long-term cost-effectiveness). The mean discounted expected QALYs over 5 years were 2.25 for NIV versus 1.82 for NIV (see *Table 27*), assuming constant health utilities beyond 6 months, resulting in an incremental QALY gain of 0.427. The QALY difference appears to be driven by higher expected survival rates over time.

Costs

Using observed 3–6 months post randomisation total costs, adjusted for covariates (e.g. age, centre, COPD status), as a basis for estimating long-term costs, the total expected (discounted) costs up to 5 years post randomisation were £12,048 for NIV compared with £9311 for IMV after assuming that long-term (beyond 6 months) resource use is equal between groups.

Incremental cost-effectiveness (base case, long-term extrapolation)

The reported NHS and PSS costs over the first 6 months were £31,711 versus £32,476 for the NIV versus IMV groups during the trial (see *Table 24*). The total expected (mean) NHS and PSS costs over 5 years were £43,759 versus £41,787 with an incremental cost of £1972 for NIV. The 5-year ICER was therefore £4618 (see *Table 27*), assuming future costs and health utilities are the same in survivors in both groups. At a cost-effectiveness threshold of £30,000 per QALY, NIV was strongly cost-effective (see *Table 27* and *Figure 23*). This is largely explained by a higher mean QALY estimate as a result of a higher survival rate in the NIV group than in the IMV group. However, the probability of cost-effectiveness of NIV is highly dependent on the assumptions about future costs and benefits beyond 6 months (see *Table 27*). Additional information might therefore be needed to reduce this decision uncertainty.

Sensitivity analyses

In the first sensitivity analyses, survival rates in the NIV group were reduced by 10% and it was assumed that costs and utilities were equal after 6 months (see *Table 38*; *Appendix 3*). This led to an incremental cost associated with NIV of £237 and a reduced incremental QALY of 0.028, with a consequent ICER of £8393 and a probability of cost-effectiveness of about 0.96 at a cost-effectiveness threshold of £30,000 per QALY (see *Table 38* in *Appendix 3*, and *Figure 24*).

If costs and health utilities for survivors are assumed to remain constant as observed in the trial (i.e. carrying forward costs and health utility values as observed at 6 months post randomisation in their groups), NIV is no longer cost-effective (mean ICER of £349,000 per additional QALY at a cost-effectiveness threshold of £30,000) (see *Table 38* in *Appendix 3*).

If, after 6 months, costs are assumed to be equal, but expected health utilities are carried forward (i.e. differ over time), the incremental cost associated with NIV falls to £2737 and the incremental QALY falls to 0.019, resulting in an ICER of £144,052 and a probability of cost-effectiveness of 2% (at a £30,000 cost-effectiveness threshold).

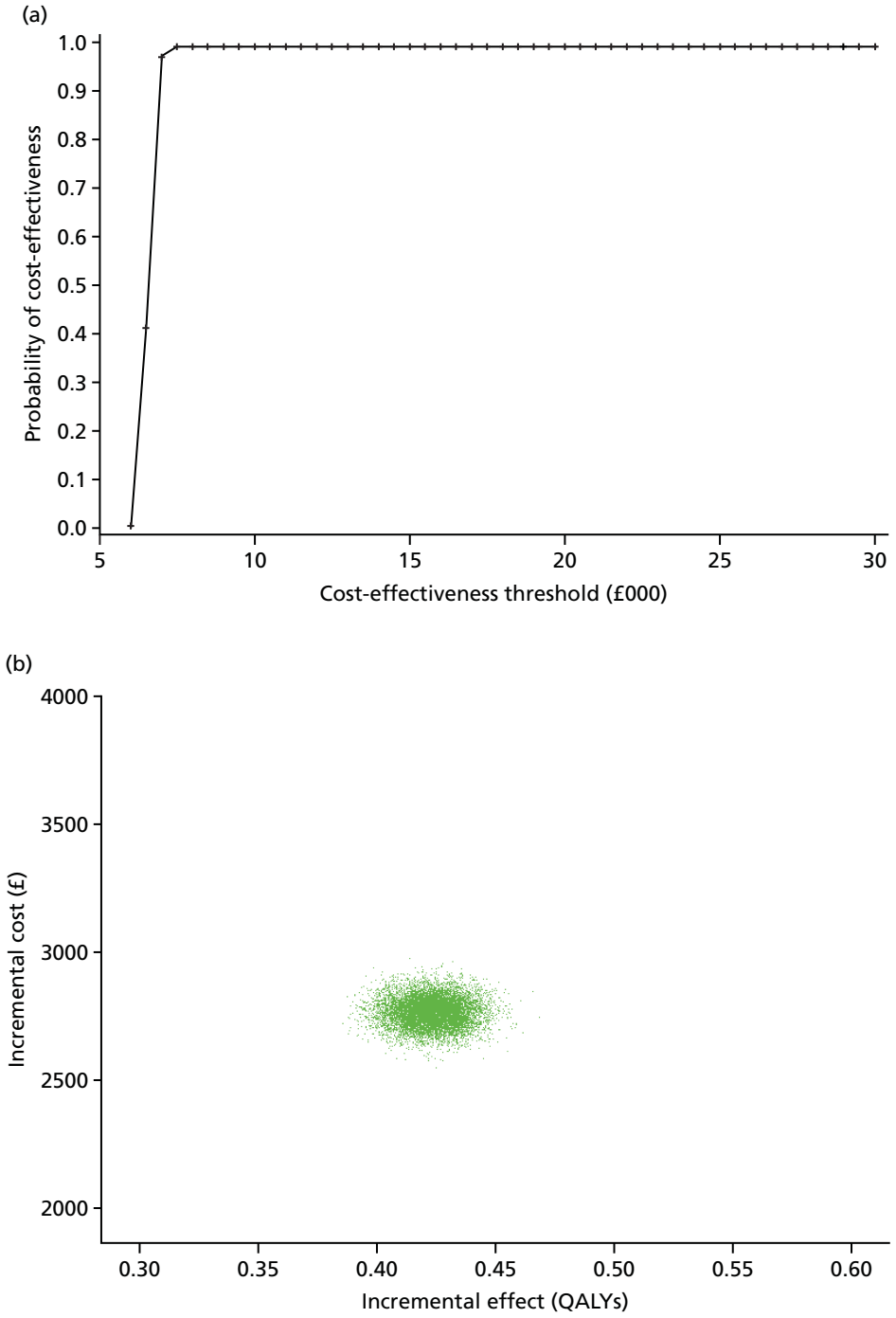


FIGURE 23 Cost-effectiveness acceptability curve and cost-effectiveness plane for long-term effectiveness (base-case long-term cost-effectiveness assuming equal future costs and effects). (a) CEAC showing the probability of cost-effectiveness of NIV at varying cost-effectiveness thresholds, assuming that future costs and effects are equal between the NIV and IMV groups; and (b) cost-effectiveness plane showing the joint distribution of projected 5-year differences in costs and QALYs between the NIV and IMV groups, assuming that costs beyond the 6-month trial period and effects are equal between groups.

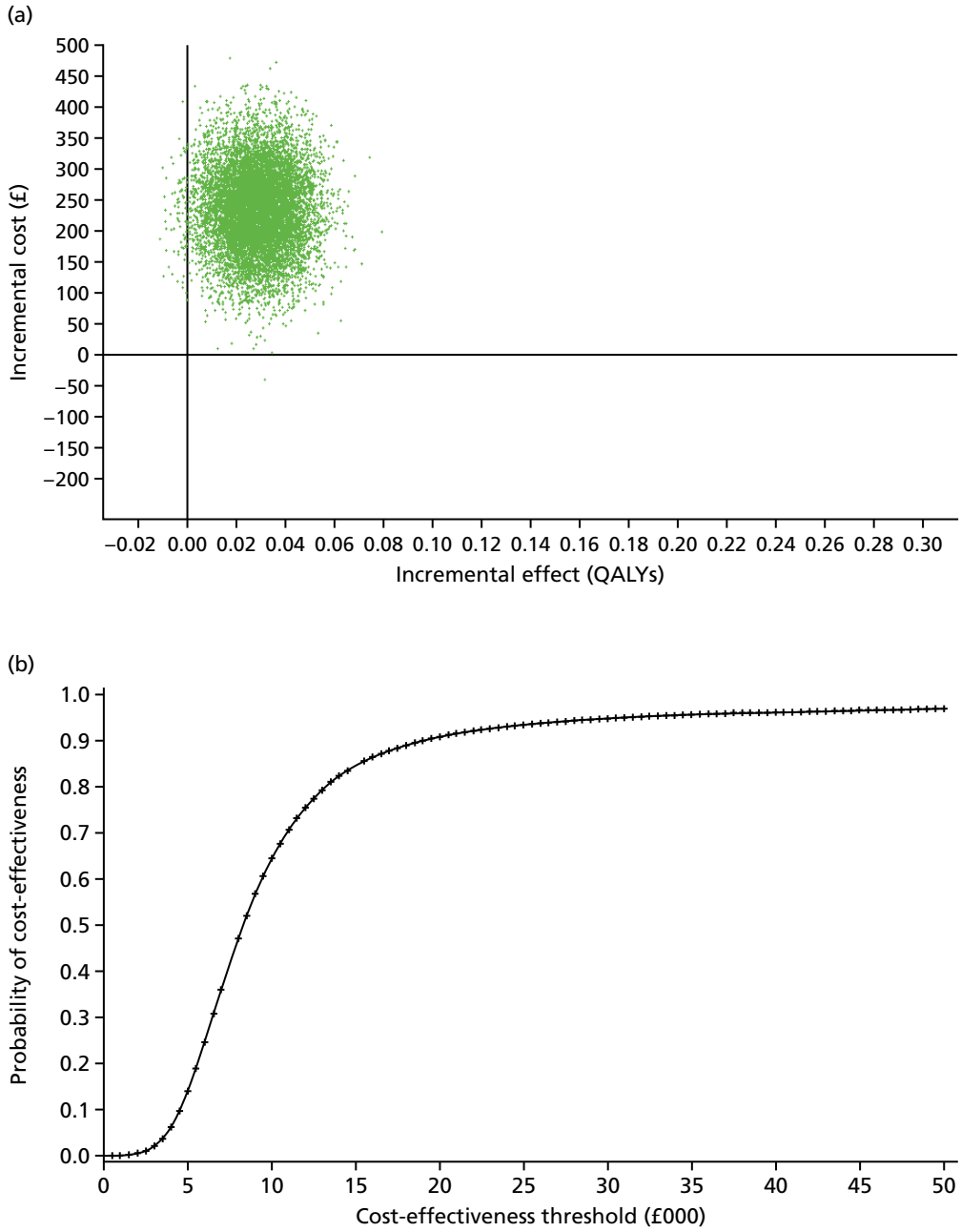


FIGURE 24 Cost-effectiveness acceptability curve and cost-effectiveness plane for long-term effectiveness (sensitivity analyses assuming that survival in the NIV group is lower by 10%). (a) Cost-effectiveness plane showing the joint distribution of projected 5-year differences in costs and QALYs between the NIV and IMV groups, assuming that survival in the NIV group is lower by 10%; and (b) CEAC showing the probability of cost-effectiveness of NIV at varying cost-effectiveness thresholds, assuming that survival in non-invasive group is lower by 10%.

Chapter 6 Discussion

Summary of main results

The Breathe pragmatic RCT compared two protocolised weaning strategies – one that promoted early extubation to NIV and one that involved sequential reduction in P_{supp} with daily SBTs prior to extubation. Early extubation to NIV had no effect on the primary outcome (liberation from ventilation) or mortality, despite a higher rate of reintubation in the NIV group than in the IMV group. The study showed clinically beneficial effects for NIV as regards reduced sedation requirements and a lower proportion of patients requiring respiratory antibiotics.

Interpretation

Despite no evidence of the effectiveness of early extubation to NIV on liberation from ventilation, these findings present useful information about the role for NIV as an intermediate step in the weaning process. Furthermore, adopting the approach outlined by Pocock and Stone,[52] a finding of no effect on the primary outcome should not be labelled as a 'negative trial'. First, the primary outcome, time from liberation from all forms of ventilation, was defined, in accordance with international guidelines, as being freedom from any form of ventilation for 48 hours after extubation. The Breathe trial found a mean difference of 2.0 days total ventilation time in favour of NIV (95% CI –4.61 to 0.69 days). The upper boundary of the CI crosses the line of no effect but the lower boundary falls below the a priori-defined minimal clinically important difference of 1 day. Owing to a lower than anticipated dropout rate (25% predicted, 17% observed), a post hoc power calculation reveals that the study had 93% power to detect the a priori-defined minimal clinically important difference of 1 day in total ventilation days. The primary outcome represents an overall measure of the effectiveness of weaning but does not account for the benefits of transitioning from IMV to NIV. This suggests that the use of NIV as a weaning strategy shows some indication of potential benefit. Second, early liberation from IMV reduces exposure to the risk of ventilator-associated lung injury and VAP. Participants in the NIV group had 3 days fewer IMV (–3.1 days, 95% CI –5.75 to –0.51 days) than those in the IMV group. This conferred additional beneficial effects including less sedation, a lower proportion of participants requiring antibiotics for presumed respiratory infection and fewer days in intensive care.

The findings from the Breathe trial add new insights to evidence from a Cochrane systematic review and meta-analysis that comprised 16 RCTs and 994 participants.[20] Unlike the Breathe trial, these were mostly small (range of 20 to 264 participants), single-centre trials and included a high proportion of participants with COPD (nine of the trials enrolled exclusively COPD participants and two enrolled predominantly COPD participants). The Breathe trial differed from these previous trials as only a small proportion (3.5%) of enrolled participants had COPD as the main indication for respiratory failure. This may reflect current UK practice, with NIV being used as a tool to prevent intubation for COPD patients. Unlike the Breathe trial, the Cochrane systematic review found strong evidence that weaning using NIV reduced mortality (RR 0.52, 95% CI 0.36 to 0.80), although moderate heterogeneity was noted.[20] Subgroup analysis showed that the beneficial effects were limited to trials that exclusively enrolled participants with COPD as the main cause of acute respiratory failure (RR 0.36, 95% CI 0.24 to 0.56). This finding is consistent with the evidence in which NIV is used to supplement usual medical care during COPD exacerbation.[53] From a pathophysiological perspective, NIV reduces respiratory muscle fatigue and tachypnoea, augments tidal volume and reduces intrinsic PEEP in patients with COPD. With the increasing adoption of NIV as a tool to prevent the need for intubation, fewer COPD patients are admitted to ICU for IMV;[6] thus, the population recruited to the Breathe trial probably better reflects contemporary ventilation practice. In addition, the Breathe trial reflects contemporary weaning practice by comparing NIV with a protocol using weaning of P_{supp}. Some of the studies included in the Cochrane report compared NIV

with a weaning protocol using a mechanical ventilation mode that incorporates mandatory ventilations, which is considered a less effective weaning strategy.

The Breathe trial evaluated NIV in patients with difficult and prolonged weaning. The 2005 international consensus conference on weaning defined difficult weaning as a failure of the initial weaning attempt and a requirement for up to three SBTs or 7 days of weaning.[7] Prolonged weaning was defined as a situation in which patients require more than three SBTs or 7 days of weaning after the first SBT.[7] In the Breathe trial, the early visual separation of the Kaplan–Meier curves over the first 7–10 days after randomisation before they later come together suggests that NIV might be most beneficial in the difficult-weaning group. This has some biological rationale as the most common causes of difficult weaning (e.g. accumulation of sedative drugs, fluid overload, respiratory muscle weakness) may be resolved more quickly than the most common underlying causes of prolonged weaning (e.g. severe/chronic cardiovascular and respiratory failure, prolonged respiratory muscle weakness).[54] To test this hypothesis, future studies might seek to prospectively identify and evaluate NIV in patients predicted to face difficult rather than prolonged weaning.

Overall, the use of NIV was well tolerated. However, the proportion of participants who failed a trial of NIV and required reintubation was twice as high in the NIV group as in the IMV group (37.4% vs. 23.1%). ICU mortality among those who required reintubation was higher (20%) than among those that did not require reintubation (6%). However, as the overall mortality rates were similar at ICU discharge (12.1% in the NIV group and 13.7% in the IMV group), death after reintubation may reflect the severity of the underlying illness as opposed to reintubation causing excess mortality per se. Other than this, the rate and patterns of AEs and SAEs were similar between groups.

Strengths and limitations

The Breathe trial benefited from several design advantages compared with previous studies on IMV and NIV. First, the use of a protocolised weaning regime in both trial groups allowed the separation of the treatment intervention from the effect of protocolised weaning.[55] The inclusion of optimised best practice guidelines (i.e. ventilation bundle, daily SBTs, tracheostomy) should reduce heterogeneity between treatment groups. Second, antibiotic use was selected as a surrogate for VAP to limit the risk of detection bias arising from different approaches to obtaining respiratory samples for culture. The trial also has important limitations. By the nature of the intervention, it was not possible to blind clinicians, participants or outcome assessors. This may have led to performance and/or detection bias. Nearly half of the participants were recruited from three large centres, which might limit generalisability. However, a sensitivity analysis found no evidence of a difference in outcomes between these three centres and the other 39 participating centres. A prerequisite for centres to participate in the Breathe trial was that they were experienced in the use of NIV. Nevertheless, it is possible that performance and outcomes may have improved as centres became more experienced in the use of the NIV weaning intervention.

Health economic evaluation

This trial-based economic evaluation revealed that the NIV protocol has some potential to be cost-effective, compared with IMV, particularly for the patients who present with COPD or do not require surgery (operative status). NIV is unlikely to be cost-effective compared with IMV for patients admitted to the ICU who do not have COPD or who require surgery. The INMB estimate was positive for the NIV protocol, a finding that remained generally robust to several sensitivity and subgroup analyses. The main reason for cost-effectiveness appears to stem from lower costs associated with the experimental group and improved effectiveness based on EQ-5D-3L-derived QALYs. However, from a NHS and PSS perspective, some costs were higher, on average, for the NIV intervention group (although not always statistically significant) than for the IMV group.

A strength of the Breathe trial was that it was prospectively designed for a cost-effectiveness analysis using individual-level data. Costs and outcomes were carefully considered in the design of this trial with the purpose of reaching a robust conclusion with respect to cost-effectiveness in a large sample of individuals. There were, however, several limitations to this cost-effectiveness analysis.

First, organ support costs after the initial 30 days were collected in such a way such that it was impossible to distinguish between the costs for multiple organs or zero or just one organ. For example, when 5 additional days were required for organ support beyond the first 30 days post randomisation, it was impossible to disentangle whether the organ support costs for these 5 days were due to the cost of supporting several organs for, for instance, the first 3 days and fewer organs for the last 2 days, or vice versa.

Second, in terms of QALYs, a baseline utility score of –0.402 was assumed, the value assigned by the EQ-5D-3L tariff to an unconscious health state, and this was considered to be the same for each participant, regardless of underlying heterogeneity in health states. This may be an unrealistic assumption, but it is in keeping with broader methodological practice for trial-based economic evaluations conducted in emergency and critical care settings.[56] Moreover, we have recently demonstrated that assuming an alternative fixed baseline utility score, for example a utility score of zero representing death, would have no effect on the area under the curve within the incremental QALY calculations.[56] Furthermore, the utility assessments performed around the point of hospital discharge required participants to reflect on their health state of at least 1 month earlier, and may, therefore, suffer from some recall bias. Consequently, the QALY values generated for the purposes of the baseline cost-effectiveness analysis were based on one fixed baseline time point and utility value. The assumption of linearity of HRQoL between data collection points is open to scrutiny and more uncertain when missing data are present.

Third, the proportion of missing data and how missingness is handled is critical as this can affect the conclusions of a cost-effectiveness analysis. In this trial, approximately 35% of QALY data and between 6% and 40% of costs (at the component level) were missing by 6 months. Had the base-case cost-effectiveness analysis considered only those individuals with complete QALY and cost data, approximately 50% of participants (with possibly informative data) would have been removed from the analysis. This approach would have probably biased the results. After investigating that the data were likely to be MAR, it seemed sensible to use MI to 'replace' missing values in order to allow a complete-case analysis using the whole data set data.

Fourth, despite the longitudinal nature of the study, resource use was retrospectively recalled by trial participants, which is also likely to result in recall bias.

Fifth, similar pilot or Phase II trials may have been useful in identifying the critical costs that drive cost-effectiveness. Instead, a broad set of NHS and PSS costs and broader societal costs were collected, some of which had little impact on the ICER values. Some costs items did not occur (e.g. see *Table 35* in *Appendix 3*) and a reduced form of such a type of data collection in this setting may be advisable with a focus on the largest and most relevant costs.

Finally, the potential for a more rigorous longer-term cost-effectiveness analysis may be needed because it appears that the effectiveness of NIV appears to deteriorate over time, reflected in shorter projected survival. The impact of non-linear extrapolation functions should be considered to assess the sensitivity of long-term cost-effectiveness.[57] This is because utility after hospital discharge may increase because of the use of additional therapies (including palliation) before declining (and may increase the QALY). A longer follow-up would have helped to reduce the uncertainty of extrapolated patient survival and patient utility. In conclusion, the data collected in the Breathe trial support a hypothesis that a NIV protocol intervention compared with an IMV protocol in this population of patients is likely to be cost-effective in the short term, particularly for some subgroups. However, initial longer-term cost-effectiveness modelling suggests that the benefits of NIV may not be cost-effective.

Patient and public involvement

In the formative stages of the trial, the Intensive Care Society's Patients and Relatives Committee helped to inform the design of the study. Guidance was provided about selecting and defining the primary and secondary end points of the trial. The group assisted us to identify the optimal timing and way to approach patients and relatives for consent, both in the early phases of the trial and during follow-up. Through ongoing involvement in the TSC, two patient and public representatives (a patient and a relative of a patient) maintained oversight of the conduct of the trial and assisted with the interpretation of the trial findings. Insights from these members highlighted the physical discomfort of a tracheal tube during weaning, an aspect of patient experience that was not captured in the design of the trial. A systematic review of qualitative studies identified physical discomfort from the endotracheal tube, suctioning and inability to communicate as common adverse patient experiences.[58] It is possible that earlier liberation from IMV may have improved patient experience; although this was not formally measured in this trial, it is a relevant outcome to consider in future studies.

Chapter 7 Conclusion

The Breathe trial, a pragmatic RCT, compared two protocolised weaning strategies in patients who failed a SBT. One strategy promoted early extubation to NIV and one involved sequential reduction in P_{supp} with daily SBTs prior to extubation. Early extubation to NIV did not reduce the overall time to liberation from ventilation. However, participants in the early extubation/NIV group spent less time receiving IMV and required less sedation and fewer respiratory antibiotics than those in the IMV group. Although the early extubation/NIV group had a higher rate of reintubation than the IMV group, there was no overall difference in AEs, SAEs or mortality. The mean incremental cost-effectiveness of the NIV intervention was estimated at £19,006 per QALY, that is, on average, the intervention was associated with a lower net cost and a higher net effect and was dominant in health economic terms. A strategy of early extubation to NIV seems to be a reasonable alternative to continuing invasive weaning procedures.

Recommendations for research

In patients who fail a SBT, which factors predict an adverse outcome (reintubation, tracheostomy, death) if extubated and weaned using NIV?

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Dipesh Mistry (Statistician, University of Warwick) contributed to the design of the work, performed the statistical analyses reported, assisted with interpretation of data and drafted the work and revised it critically for important intellectual content.

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Beverly Hoddell (Trial Manager, University of Warwick) co-ordinated the trial and was involved in the design of the study, acquisition of data and revised the work critically for important intellectual content.

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Sukhdeep Dosanjh (Senior Project Manager, University of Warwick) was involved in the design of the study, acquisition of data and revised the work critically for important intellectual content.

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Keith Couper (Research Nurse, Heartlands Hospital) was involved in the design of the study, acquisition of data and revised the work critically for important intellectual content.

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J Duncan Young (Professor of Intensive Care Medicine, University of Oxford) was involved in the conception and design of the work, contributed to the acquisition and interpretation of the data and revised the work critically for important intellectual content.

Tim Walsh (Professor of Intensive Care Medicine, University of Edinburgh) was involved in the conception and design of the work, contributed to the acquisition and interpretation of the data and revised the work critically for important intellectual content.

Bronagh Blackwood (Professor, Queen's University, Belfast) was Principal Investigator at Royal Victoria Hospital, Belfast, and was involved in the conception and design of the work, contributed to the acquisition and interpretation of the data and revised the work critically for important intellectual content.

Louise Rose (Co-investigator) provided clinical expertise and support to the trial teams.

Sarah E Lamb (Professor, University of Oxford) was involved in the conception and design of the work, contributed to the acquisition and interpretation of the data and revised the work critically for important intellectual content.

Melina Dritsaki (Health Economist, University of Warwick) contributed to the design of the economic research instruments and the collection of unit cost data.

Mandy Maredza (Health Economist, University of Warwick) contributed to the design of the economic research instruments and the collection of unit cost data.

Iftekhar Khan (Health Economist, University of Warwick) conducted the main body of the analyses of the health economic data.

Stavros Petrou (Professor of Health Economics, University of Warwick) provided oversight of all aspects of the economic evaluation including its design, conduct, analysis and reporting.

Simon Gates (Professor, University of Warwick) was involved in the conception and design of the work, contributed to the acquisition and interpretation of the data and revised the work critically for important intellectual content.

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Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to available anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Summary of screening

TABLE 28 Summary of screening of patients through to randomisation

Site name	Number screened	Excluded from trial, *n* (%)	Had SBT, *n* (%)	Failed SBT, *n* (%)	Randomised patients, *n* (%)
Addenbrooke's	792	666 (84)	126 (16)	35 (28)	19 (2)
Basildon	73	62 (85)	11 (15)	1 (9)	1 (1)
Bedford	308	258 (84)	50 (16)	4 (8)	3 (1)
BHH	609	463 (76)	146 (24)	60 (34)	60 (10)
Blackpool	291	278 (96)	13 (4)	6 (50)	6 (2)
Bradford RI	270	246 (91)	24 (9)	10 (42)	9 (3)
Bristol RI	199	174 (87)	25 (13)	0 (0)	0 (0)
Broomfield	90	82 (91)	8 (9)	0 (0)	0 (0)
Edinburgh RI	330	317 (96)	13 (4)	4 (31)	3 (1)
Forth Valley	132	100 (76)	32 (24)	0 (0)	0 (0)
Freeman	175	166 (95)	9 (5)	2 (22)	1 (1)
George Eliot	86	80 (93)	6 (7)	3 (50)	2 (2)
Glenfield	99	91 (92)	8 (8)	2 (25)	2 (2)
Hillingdon	85	56 (66)	29 (34)	14 (48)	13 (15)
Hull RI	393	375 (95)	18 (5)	2 (11)	1 (0)
James Paget	95	93 (98)	2 (2)	0 (0)	0 (0)
John Radcliffe	93	60 (65)	33 (35)	1 (3)	0 (0)
King's Lynn QE	137	117 (85)	20 (15)	8 (40)	7 (5)
Leicester RI	291	271 (93)	20 (7)	6 (30)	5 (2)
Leighton	226	212 (94)	14 (6)	3 (21)	3 (1)
Manchester RI	566	503 (89)	63 (11)	9 (14)	6 (1)
Milton Keynes	154	148 (96)	6 (4)	1 (17)	1 (1)
Monklands	223	223 (100)	0 (0)	0 (0)	0 (0)
Musgrove Park	206	187 (91)	19 (9)	4 (21)	4 (2)
New Cross	256	211 (82)	45 (18)	6 (13)	2 (1)
Papworth	127	125 (98)	2 (2)	0 (0)	0 (0)
Peterborough	258	235 (91)	23 (9)	13 (57)	13 (5)
Poole	373	336 (90)	37 (10)	4 (11)	3 (1)
Portsmouth	335	328 (98)	7 (2)	2 (29)	2 (1)
QEHB	1838	1618 (88)	220 (12)	71 (32)	51 (3)
Royal Blackburn	572	545 (95)	27 (5)	3 (11)	6 (1)
Royal Gwent	187	173 (93)	14 (7)	5 (36)	4 (2)
Royal Liverpool	425	375 (88)	50 (12)	10 (20)	8 (2)

continued

TABLE 28 Summary of screening of patients through to randomisation (*continued*)

Site name	Number screened	Excluded from trial, *n* (%)	Had SBT, *n* (%)	Failed SBT, *n* (%)	Randomised patients, *n* (%)
Royal Surrey	71	68 (96)	3 (4)	1 (33)	0 (0)
Royal Sussex	486	465 (96)	21 (4)	3 (14)	3 (1)
Russells Hall	105	73 (70)	32 (30)	11 (34)	7 (7)
RVH Belfast	1106	870 (79)	236 (21)	21 (9)	12 (1)
RVI Newcastle	567	558 (98)	9 (2)	2 (22)	2 (0)
Southampton	409	400 (98)	9 (2)	4 (44)	5 (1)
Southend	13	13 (100)	0 (0)	0 (0)	0 (0)
St James's Leeds	409	371 (91)	38 (9)	14 (37)	15 (4)
St Thomas' London	1054	950 (90)	104 (10)	45 (43)	50 (5)
UHCW	380	358 (94)	22 (6)	2 (9)	2 (1)
UHNS	427	417 (98)	10 (2)	4 (40)	3 (1)
UHOW	745	710 (95)	35 (5)	10 (29)	8 (1)
UHSM	138	127 (92)	11 (8)	1 (9)	1 (1)
Western General	452	399 (88)	53 (12)	12 (23)	8 (2)
West Middlesex	101	96 (95)	5 (5)	2 (40)	2 (2)
Wexham Park	65	58 (89)	7 (11)	2 (29)	0 (0)
Yeovil	69	66 (96)	3 (4)	1 (33)	1 (1)
York	235	201 (86)	34 (14)	18 (53)	10 (4)
Total	17,126	15,374 (90)	1752 (10)	432 (25)	364 (2)

QE, Queen Elizabeth; RI, Royal Infirmary; RVH, Royal Victoria Hospital; RVI, Royal Victoria Infirmary; UHCW, University Hospital Coventry and Warwickshire; UHNS, University Hospitals of North Midlands; UHOW, University Hospital of Wales; UHSM, University Hospital of South Manchester.

TABLE 29 Summary of reasons why patients were not randomised

Site name	Number screened	Not meeting inclusion criteria, *n* (%)		Meeting exclusion criteria, *n* (%)								Other reasons for exclusion	SBT process, *n* (%)	
		Aged > 16 years	Passed SBT	Pregnant	Tracheostomy	Neurological deficit	NIV contraindication	Home ventilation	Withdrawal/ patient died	Further surgery/ procedure requiring sedation planned in next 48 hours	Previous participation in the Breathe trial		Had SBT (patients who are ready for weaning)	Failed SBT
Addenbrooke's	792	0 (0)	91 (72)	0 (0)	212 (27)	115 (15)	78 (10)	9 (1)	189 (24)	4 (1)	1 (0)	58 (7)	126 (16)	35 (4)
Basildon	73	0 (0)	10 (91)	0 (0)	5 (7)	33 (45)	6 (8)	0 (0)	18 (25)	0 (0)	0 (0)	0 (0)	11 (15)	1 (1)
Bedford	308	21 (4)	46 (92)	3 (1)	36 (12)	21 (7)	4 (1)	0 (0)	138 (45)	2 (1)	1 (0)	32 (10)	50 (16)	4 (1)
BHH	609	0 (0)	96 (66)	1 (0)	97 (16)	18 (3)	41 (7)	0 (0)	162 (27)	1 (0)	3 (0)	139 (23)	146 (24)	50 (8)
Blackpool	291	2 (0)	7 (54)	2 (0)	114 (39)	14 (5)	46 (16)	0 (0)	82 (28)	0 (0)	0 (0)	18 (6)	13 (4)	6 (2)
Bradford RI	270	0 (0)	14 (58)	0 (0)	82 (30)	21 (8)	7 (3)	0 (0)	125 (46)	0 (0)	1 (0)	10 (4)	24 (9)	10 (4)
Bristol RI	199	0 (0)	25 (100)	0 (0)	52 (26)	13 (7)	2 (1)	0 (0)	11 (6)	6 (3)	1 (1)	89 (45)	25 (13)	0 (0)
Broomfield	90	0 (0)	8 (100)	0 (0)	33 (37)	7 (8)	8 (9)	0 (0)	18 (20)	2 (2)	0 (0)	14 (16)	8 (9)	0 (0)
Edinburgh RI	330	1 (0)	9 (69)	0 (0)	49 (15)	44 (13)	22 (7)	3 (1)	114 (35)	0 (0)	0 (0)	84 (25)	13 (4)	4 (1)
Forth Valley	132	4 (2)	32 (100)	0 (0)	20 (15)	4 (3)	7 (5)	7 (5)	50 (38)	1 (1)	0 (0)	7 (5)	32 (24)	0 (0)
Freeman	175	0 (0)	7 (78)	0 (0)	54 (31)	16 (9)	12 (7)	0 (0)	57 (33)	2 (1)	0 (0)	25 (14)	9 (5)	2 (1)
George Eliot	86	0 (0)	3 (50)	0 (0)	37 (43)	0 (0)	11 (13)	0 (0)	26 (30)	1 (1)	0 (0)	5 (6)	6 (7)	3 (3)
Glenfield	99	0 (0)	6 (75)	0 (0)	50 (51)	11 (11)	5 (5)	0 (0)	11 (11)	1 (1)	0 (0)	13 (13)	8 (8)	2 (2)
Hillingdon	85	0 (0)	15 (52)	0 (0)	12 (14)	9 (11)	8 (9)	0 (0)	16 (19)	0 (0)	0 (0)	11 (13)	29 (34)	14 (16)
Hull RI	393	11 (1)	16 (89)	0 (0)	96 (24)	63 (16)	21 (5)	0 (0)	170 (43)	0 (0)	0 (0)	13 (3)	18 (5)	2 (1)
James Paget	95	5 (3)	2 (100)	2 (2)	25 (26)	3 (3)	1 (1)	0 (0)	50 (53)	0 (0)	0 (0)	7 (7)	2 (2)	0 (0)
John Radcliffe	93	0 (0)	32 (97)	0 (0)	11 (12)	11 (12)	1 (1)	0 (0)	8 (9)	7 (8)	0 (0)	22 (24)	33 (35)	1 (1)
King's Lynn QE	137	1 (0)	12 (60)	0 (0)	15 (11)	8 (20)	3 (2)	0 (0)	63 (46)	1 (1)	0 (0)	26 (19)	20 (15)	8 (6)
Leicester RI	291	0 (0)	14 (70)	0 (0)	76 (26)	52 (18)	37 (13)	1 (0)	62 (21)	5 (2)	0 (0)	38 (13)	20 (7)	6 (2)
Leighton	226	1 (0)	11 (79)	0 (0)	18 (8)	15 (7)	14 (6)	0 (0)	141 (62)	0 (0)	0 (0)	23 (10)	14 (6)	3 (1)
Manchester RI	566	0 (0)	54 (86)	2 (1)	114 (20)	170 (30)	37 (7)	0 (0)	125 (22)	4 (1)	2 (0)	49 (9)	63 (11)	9 (2)
Milton Keynes	154	2 (1)	5 (83)	0 (0)	28 (18)	2 (1)	0 (0)	0 (0)	104 (68)	0 (0)	0 (0)	12 (8)	6 (4)	1 (1)

continued

TABLE 29 Summary of reasons why patients were not randomised (*continued*)

Site name	Number screened	Not meeting inclusion criteria, *n* (%)		Meeting exclusion criteria, *n* (%)								Other reasons for exclusion	SBT process, *n* (%)	
		Aged > 16 years	Passed SBT	Pregnant	Tracheostomy	Neurological deficit	NIV contraindication	Home ventilation	Withdrawal/ patient died	Further surgery/ procedure requiring sedation planned in next 48 hours	Previous participation in the Breathe trial		Had SBT (patients who are ready for weaning)	Failed SBT
Monklands	223	1 (0)	0 (0)	0 (0)	48 (22)	18 (8)	13 (6)	0 (0)	103 (46)	5 (2)	0 (0)	35 (16)	0 (0)	0 (0)
Musgrove Park	206	10 (2)	15 (79)	0 (0)	16 (8)	17 (8)	15 (7)	3 (1)	95 (46)	1 (0)	0 (0)	30 (15)	19 (9)	4 (2)
New Cross	256	0 (0)	39 (87)	0 (0)	62 (24)	21 (27)	8 (3)	0 (0)	99 (39)	1 (0)	1 (0)	19 (7)	45 (18)	6 (2)
Papworth	127	0 (0)	2 (100)	0 (0)	30 (24)	1 (7)	12 (9)	0 (0)	25 (20)	2 (2)	0 (0)	55 (43)	2 (2)	0 (0)
Peterborough	258	3 (1)	10 (43)	1 (0)	62 (24)	19 (18)	11 (4)	0 (0)	94 (36)	0 (0)	0 (0)	45 (17)	23 (9)	13 (5)
Poole	373	1 (0)	33 (89)	1 (0)	67 (18)	67 (5)	85 (23)	3 (1)	76 (20)	0 (0)	0 (0)	36 (10)	37 (10)	4 (1)
Portsmouth	335	21 (3)	5 (71)	0 (0)	55 (16)	16 (6)	24 (7)	0 (0)	142 (42)	0 (0)	0 (0)	70 (21)	7 (2)	2 (1)
QEHB	1838	1 (0)	149 (68)	2 (0)	633 (34)	361 (5)	41 (2)	0 (0)	264 (14)	6 (0)	4 (0)	306 (17)	220 (12)	71 (4)
Royal Blackburn	572	1 (0)	24 (89)	3 (0)	176 (31)	26 (20)	12 (2)	8 (1)	277 (48)	1 (0)	0 (0)	41 (7)	27 (5)	3 (1)
Royal Gwent	187	0 (0)	9 (64)	0 (0)	44 (24)	43 (23)	1 (1)	0 (0)	82 (44)	0 (0)	2 (1)	1 (1)	14 (7)	5 (3)
Royal Liverpool	425	1 (0)	40 (80)	0 (0)	62 (15)	83 (5)	36 (8)	2 (0)	136 (32)	1 (0)	1 (0)	53 (12)	50 (12)	10 (2)
Royal Surrey	71	0 (0)	2 (67)	0 (0)	16 (23)	10 (20)	18 (25)	2 (3)	14 (20)	0 (0)	0 (0)	8 (11)	3 (4)	1 (1)
Royal Sussex	486	0 (0)	18 (86)	0 (0)	175 (36)	24 (14)	14 (3)	1 (0)	224 (46)	0 (0)	0 (0)	27 (6)	21 (4)	3 (1)
Russells Hall	105	0 (0)	21 (66)	0 (0)	6 (6)	19 (5)	10 (10)	1 (1)	25 (24)	0 (0)	0 (0)	12 (11)	32 (30)	11 (10)
RVH Belfast	1106	16 (1)	215 (91)	1 (0)	204 (18)	98 (18)	12 (1)	1 (0)	358 (32)	3 (0)	0 (0)	177 (16)	236 (21)	21 (2)
Newcastle RVI	567	1 (0)	7 (78)	0 (0)	133 (23)	155 (1)	55 (10)	5 (1)	172 (30)	5 (1)	0 (0)	32 (6)	9 (2)	2 (0)
Southampton	409	1 (0)	5 (56)	0 (0)	59 (14)	62 (9)	40 (10)	0 (0)	164 (40)	8 (2)	0 (0)	66 (16)	9 (2)	4 (1)
Southend	13	0 (0)	0 (0)	0 (0)	1 (8)	4 (15)	1 (8)	0 (0)	3 (23)	0 (0)	0 (0)	4 (31)	0 (0)	0 (0)
St James's Leeds	409	0 (0)	24 (63)	0 (0)	105 (26)	85 (31)	13 (3)	4 (1)	134 (33)	0 (0)	3 (1)	27 (7)	38 (9)	14 (3)
St Thomas' London	1054	5 (0)	59 (57)	10 (1)	300 (28)	82 (21)	59 (6)	9 (1)	292 (28)	2 (0)	1 (0)	190 (18)	104 (10)	45 (4)

Site name	Number screened	Not meeting inclusion criteria, *n* (%)		Meeting exclusion criteria, *n* (%)									SBT process, *n* (%)	
		Aged > 16 years	Passed SBT	Pregnant	Tracheostomy	Neurological deficit	NIV contraindication	Home ventilation	Withdrawal/ patient died	Further surgery/ procedure requiring sedation planned in next 48 hours	Previous participation in the Breathe trial	Other reasons for exclusion	Had SBT (patients who are ready for weaning)	Failed SBT
UHCW	380	0 (0)	20 (91)	0 (0)	98 (26)	53 (8)	22 (6)	1 (0)	81 (21)	0 (0)	0 (0)	103 (27)	22 (6)	2 (1)
UHNS	427	0 (0)	6 (60)	0 (0)	127 (30)	156 (14)	15 (4)	0 (0)	92 (22)	1 (0)	0 (0)	26 (6)	10 (2)	4 (1)
UHOW	745	1 (0)	25 (71)	1 (0)	101 (14)	168 (37)	121 (16)	3 (0)	273 (37)	0 (0)	0 (0)	42 (6)	35 (5)	10 (1)
UHSM	138	0 (0)	10 (91)	0 (0)	59 (43)	17 (23)	11 (8)	2 (1)	38 (28)	0 (0)	0 (0)	0 (0)	11 (8)	1 (1)
Western General	452	5 (1)	41 (77)	0 (0)	57 (13)	209 (8)	12 (3)	10 (2)	83 (18)	0 (0)	0 (0)	23 (5)	53 (12)	12 (3)
West Middlesex	101	0 (0)	3 (60)	0 (0)	25 (25)	8 (12)	3 (3)	0 (0)	52 (51)	1 (1)	1 (1)	6 (6)	5 (5)	2 (2)
Wexham Park	65	0 (0)	5 (71)	0 (0)	16 (25)	6 (46)	4 (6)	1 (2)	28 (43)	0 (0)	0 (0)	3 (5)	7 (11)	2 (3)
Yeovil	69	0 (0)	2 (67)	0 (0)	3 (4)	9 (9)	11 (16)	0 (0)	41 (59)	0 (0)	0 (0)	2 (3)	3 (4)	1 (1)
York	235	0 (0)	16 (47)	0 (0)	26 (11)	28 (13)	16 (7)	1 (0)	104 (44)	3 (1)	0 (0)	23 (10)	34 (14)	18 (8)
Total	17,126	116 (1)	1320 (75)	29 (0)	4002 (23)	2515 (12)	1066 (10)	77 (1)	5311 (24)	79 (1)	22 (0)	2157 (7)	1752 (10)	432 (4)

QE, Queen Elizabeth; RI, Royal Infirmary; RVH, Royal Victoria Hospital; RVI, Royal Victoria Infirmary; UHCW, University Hospital Coventry and Warwickshire; UHNS, University Hospitals of North Midlands; UHOW, University Hospital of Wales; UHSM, University Hospital of South Manchester.

TABLE 30 Summary of other reasons why patients were excluded from the screening process

Site name	Number screened	Other reasons for exclusion, *n* (%)					
		Consultant refusal	Patient refusal	Relative refused	Other studies	Total other exclusions	Blanks, missing data
Addenbrooke's	792	5 (1)	0 (0)	2 (0)	15 (2)	28 (4)	8 (1)
Basildon	73	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Bedford	308	0 (0)	0 (0)	0 (0)	0 (0)	32 (10)	0 (0)
BHH	609	10 (2)	0 (0)	5 (1)	9 (1)	23 (4)	92 (15)
Blackpool	291	1 (0)	0 (0)	0 (0)	4 (1)	13 (4)	0 (0)
Bradford RI	270	1 (0)	0 (0)	5 (2)	0 (0)	4 (1)	0 (0)
Bristol RI	199	7 (4)	0 (0)	0 (0)	20 (10)	23 (12)	39 (20)
Broomfield	90	2 (2)	0 (0)	4 (4)	0 (0)	4 (4)	4 (4)
Edinburgh RI	330	24 (7)	0 (0)	7 (2)	15 (5)	36 (11)	2 (1)
Forth Valley	132	0 (0)	0 (0)	2 (2)	0 (0)	5 (4)	0 (0)
Freeman	175	6 (3)	0 (0)	4 (2)	0 (0)	14 (8)	1 (1)
George Eliot	86	1 (1)	0 (0)	0 (0)	0 (0)	4 (5)	0 (0)
Glenfield	99	1 (1)	0 (0)	4 (4)	2 (2)	6 (6)	0 (0)
Hillingdon	85	0 (0)	1 (1)	5 (6)	0 (0)	5 (6)	0 (0)
Hull RI	393	2 (1)	0 (0)	0 (0)	0 (0)	11 (3)	0 (0)
James Paget	95	1 (1)	0 (0)	0 (0)	0 (0)	5 (5)	1 (1)
John Radcliffe	93	3 (3)	0 (0)	0 (0)	0 (0)	5 (5)	14 (15)
King's Lynn QE	137	3 (2)	0 (0)	15 (11)	0 (0)	6 (4)	2 (1)
Leicester RI	291	13 (4)	0 (0)	2 (1)	0 (0)	23 (8)	0 (0)
Leighton	226	0 (0)	4 (2)	7 (3)	0 (0)	12 (5)	0 (0)
Manchester RI	566	24 (4)	1 (0)	7 (1)	2 (0)	14 (2)	1 (0)
Milton Keynes	154	3 (2)	0 (0)	1 (1)	0 (0)	8 (5)	0 (0)
Monklands	223	14 (6)	2 (1)	0 (0)	0 (0)	19 (9)	0 (0)
Musgrove Park	206	10 (5)	0 (0)	5 (2)	1 (0)	14 (7)	0 (0)
New Cross	256	0 (0)	0 (0)	1 (0)	4 (2)	13 (5)	1 (0)
Papworth	127	6 (5)	1 (1)	3 (2)	5 (4)	40 (31)	0 (0)
Peterborough	258	5 (2)	1 (0)	15 (6)	1 (0)	23 (9)	0 (0)
Poole	373	7 (2)	1 (0)	14 (4)	2 (1)	12 (3)	0 (0)
Portsmouth	335	3 (1)	0 (0)	11 (3)	2 (1)	47 (14)	7 (2)
QEHB	1838	17 (1)	8 (0)	5 (0)	18 (1)	210 (11)	48 (3)
Royal Blackburn	572	6 (1)	0 (0)	2 (0)	2 (0)	31 (5)	0 (0)
Royal Gwent	187	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Royal Liverpool	425	4 (1)	1 (0)	36 (8)	0 (0)	12 (3)	0 (0)
Royal Surrey	71	5 (7)	0 (0)	0 (0)	0 (0)	3 (4)	0 (0)
Royal Sussex	486	0 (0)	1 (0)	3 (1)	6 (1)	17 (3)	0 (0)
Russells Hall	105	2 (2)	0 (0)	3 (3)	0 (0)	6 (6)	1 (1)

TABLE 30 Summary of other reasons why patients were excluded from the screening process (*continued*)

Site name	Number screened	Other reasons for exclusion, *n* (%)					
		Consultant refusal	Patient refusal	Relative refused	Other studies	Total other exclusions	Blanks, missing data
RVH Belfast	1106	2 (0)	0 (0)	2 (0)	18 (2)	125 (11)	30 (3)
RVI Newcastle	567	7 (1)	2 (0)	5 (1)	0 (0)	18 (3)	0 (0)
Southampton	409	1 (0)	0 (0)	4 (1)	5 (1)	56 (14)	0 (0)
Southend	13	0 (0)	0 (0)	0 (0)	0 (0)	4 (31)	0 (0)
St James's Leeds	409	3 (1)	0 (0)	0 (0)	1 (0)	8 (2)	15 (4)
St Thomas' London	1054	15 (1)	3 (0)	15 (1)	61 (6)	80 (8)	16 (2)
UHCW	380	7 (2)	0 (0)	1 (0)	14 (4)	11 (3)	70 (18)
UHNS	427	3 (1)	0 (0)	2 (0)	10 (2)	11 (3)	0 (0)
UHOW	745	7 (1)	1 (0)	4 (1)	3 (0)	27 (4)	0 (0)
UHSM	138	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Western General	452	1 (0)	0 (0)	2 (0)	0 (0)	20 (4)	0 (0)
West Middlesex	101	0 (0)	0 (0)	0 (0)	0 (0)	6 (6)	0 (0)
Wexham Park	65	0 (0)	0 (0)	1 (2)	0 (0)	2 (3)	0 (0)
Yeovil	69	0 (0)	0 (0)	0 (0)	0 (0)	2 (3)	0 (0)
York	235	2 (1)	3 (1)	9 (4)	0 (0)	9 (4)	0 (0)
Total	17,126	234 (1)	30 (0)	213 (0)	220 (2)	1108 (4)	352 (1)

QE, Queen Elizabeth; RI, Royal Infirmary; RVH, Royal Victoria Hospital; RVI, Royal Victoria Infirmary; UHCW, University Hospital Coventry and Warwickshire; UHNS, University Hospitals of North Midlands; UHOW, University Hospital of Wales; UHSM, University Hospital of South Manchester.

Appendix 2 Randomised participants by site and treatment

TABLE 31 Randomised participants by site and treatment

Site name	Trial group, *n* (%)		Total (*N* = 364), *n* (%)
	Invasive weaning (*N* = 182)	Non-invasive weaning (*N* = 182)	
Addenbrooke's	10 (5)	9 (5)	19 (5)
Basildon	0	1 (1)	1 (0)
Bedford	1 (1)	2 (1)	3 (1)
BHH	30 (16)	30 (16)	60 (16)
Blackpool	3 (2)	3 (2)	6 (2)
Bradford RI	4 (2)	5 (3)	9 (2)
Edinburgh RI	1 (1)	2 (1)	3 (1)
Freeman	0	1 (1)	1 (0)
George Eliot	0	2 (1)	2 (1)
Glenfield	1 (1)	1 (1)	2 (1)
Hillingdon	7 (4)	6 (3)	13 (4)
Hull RI	0	1 (1)	1 (0)
King's Lynn QE	3 (2)	4 (2)	7 (2)
Leicester RI	2 (1)	3 (2)	5 (1)
Leighton	1 (1)	2 (1)	3 (1)
Manchester RI	3 (2)	3 (2)	6 (2)
Milton Keynes	1 (1)	0	1 (0)
Musgrove Park	2 (1)	2 (1)	4 (1)
New Cross	1 (1)	1 (1)	2 (1)
Peterborough	7 (4)	6 (3)	13 (4)
Poole	1 (1)	2 (1)	3 (1)
Portsmouth	1 (1)	1 (1)	2 (1)
QEHB	26 (14)	25 (14)	51 (14)
Royal Blackburn	3 (2)	3 (2)	6 (2)
Royal Gwent	2 (1)	2 (1)	4 (1)
Royal Liverpool	4 (2)	4 (2)	8 (2)
Royal Sussex	2 (1)	1 (1)	3 (1)
Russells Hall	4 (2)	3 (2)	7 (2)
RVH Belfast	6 (3)	6 (3)	12 (3)
RVI Newcastle	1 (1)	1 (1)	2 (1)
Southampton	2 (1)	3 (2)	5 (1)

continued

TABLE 31 Randomised participants by site and treatment (*continued*)

Site name	Trial group, *n* (%)		Total (*N* = 364), *n* (%)
	Invasive weaning (*N* = 182)	Non-invasive weaning (*N* = 182)	
St James's Leeds	9 (5)	6 (3)	15 (4)
St Thomas' London	26 (14)	24 (13)	50 (14)
UHCW	2 (1)	0	2 (1)
UHNS	1 (1)	2 (1)	3 (1)
UHOW	4 (2)	4 (2)	8 (2)
UHSM	1 (1)	0	1 (0)
Western General	4 (2)	4 (2)	8 (2)
West Middlesex	0	2 (1)	2 (1)
Yeovil	1 (1)	0	1 (0)
York	5 (3)	5 (3)	10 (3)

QE, Queen Elizabeth; RI, Royal Infirmary; RVH, Royal Victoria Hospital; RVI, Royal Victoria Infirmary; UHCW, University Hospital Coventry and Warwickshire; UHNS, University Hospitals of North Midlands; UHOW, University Hospital of Wales; UHSM, University Hospital of South Manchester.

TABLE 32 Randomised participants by randomisation strata and treatment

Site name	Absence of COPD				Presence of COPD			
	Non-operative		Postoperative		Non-operative		Postoperative	
	Invasive weaning	Non-invasive weaning	Invasive weaning	Non-invasive weaning	Invasive weaning	Non-invasive weaning	Invasive weaning	Non-invasive weaning
Addenbrooke's	4	6	5	1	–	–	1	2
Basildon	–	1	–	–	–	–	–	–
Bedford	1	–	–	1	–	1	–	–
BHH	18	21	5	7	7	1		1
Blackpool	2	3	–	–	1	–	–	–
Bradford RI	3	3	–	2	–	–	1	–
Edinburgh RI	–	1	1	–	–	1	–	–
Freeman	–	1	–	–	–	–	–	–
George Eliot	–	1	–	–	–	1	–	–
Glenfield	–	–	–	1	–	–	1	–
Hillingdon	3	3	3	1	1	2		
Hull RI	–	–	–	1	–	–	–	–
King's Lynn QE	1	2	–	1	2	1	–	–
Leicester RI	2	1	–	1	–	1	–	–
Leighton	1	2	–	–	–	–	–	–
Manchester RI	2	2	–	1	1	–	–	–
Milton Keynes	–	–	1	–	–	–	–	–
Musgrove Park	1	1	1	–	–	1	–	–

TABLE 32 Randomised participants by randomisation strata and treatment (*continued*)

	Absence of COPD				Presence of COPD			
	Non-operative		Postoperative		Non-operative		Postoperative	
Site name	Invasive weaning	Non-invasive weaning	Invasive weaning	Non-invasive weaning	Invasive weaning	Non-invasive weaning	Invasive weaning	Non-invasive weaning
New Cross	–	–	1	–	–	1	–	–
Peterborough	6	4	1	1	–	–	–	1
Poole	1	2	–	–	–	–	–	–
Portsmouth	–	1	–	–	1	–	–	–
QEHB	14	13	11	8	1	3		1
Royal Blackburn	2	1	–	1	–	1	1	–
Royal Gwent	2	1	–	–	–	1	–	–
Royal Liverpool	1	2	2	1	–	1	1	–
Royal Sussex	–	1	2	–	–	–	–	–
Russells Hall	4	2	–	1	–	–	–	–
RVH Belfast	4	2	–	3	–	–	2	1
RVI Newcastle	1	–	–	–	–	1	–	–
Southampton	1	2	1	1	–	–	–	–
St James's Leeds	4	3	3	2	2	1	–	–
St Thomas' London	15	11	7	11	3	1	1	1
UHCW	–	–	2	–	–	–	–	–
UHNS	1	–	–	–	–	2	–	–
UHOW	3	2	1	1	–	1	–	–
UHSM	–	–	–	–	–	–	1	–
Western General	4	1	–	2	–	1	–	–
West Middlesex	–	1	–	–	–	1	–	–
Yeovil	–	–	–	–	1	–	–	–
York	2	5	–	–	3	–	–	–
Total	103	102	47	49	23	24	9	7

QE, Queen Elizabeth; RI, Royal Infirmary; RVH, Royal Victoria Hospital; RVI, Royal Victoria Infirmary; UHCW, University Hospital Coventry and Warwickshire; UHNS, University Hospitals of North Midlands; UHOW, University Hospital of Wales; UHSM, University Hospital of South Manchester.

Appendix 3 Health economics tables

TABLE 33 Derivation of expected costs (discounted raw data)

Time (months)	NIV survival rate	IMV survival rate	NIV expected costs (equal resource use)[a] (£)	IMV expected costs (£)	NIV expected costs[b] (£)
0	1	1	Use observed	Use observed	Use observed
3	0.79	0.76	Use observed	Use observed	Use observed
6	0.76	0.70	Use observed	Use observed	Use observed
9	0.75	0.67	801	716	1056
12	0.74	0.64	790	684	1042
15	0.73	0.61	728	608	959
18	0.72	0.60	717	598	946
21	0.71	0.58	708	578	933
24	0.71	0.56	708	558	933
27	0.70	0.55	674	529	889
30	0.70	0.54	674	520	889
33	0.69	0.53	665	511	876
36	0.69	0.52	665	501	876
39	0.69	0.51	642	475	847
42	0.68	0.50	633	465	834
45	0.68	0.49	633	456	834
48	0.68	0.48	602	447	834
51	0.67	0.47	602	423	794
54	0.67	0.47	602	423	794
57	0.67	0.46	602	414	794
60	0.67	0.45	602	405	794
Total			12,048	9311	15,924

a Assuming IMV and NIV future (after 6 months) health resource use are equal (only extrapolate costs > 6 months included in estimates).
b Assuming future costs on the NIV are carried forward (as observed).
Note
All costs after 1 year were discounted at 3.5% per annum.

TABLE 34 Summary of longer-term cost-effectiveness analyses scenarios

Analyses	Survival	Utilities between groups	Costs between groups
1. Primary	Different between groups	Equal between groups after 6 months (set NIV = IMV)	Equal between groups after 6 months (set NIV = IMV)
Sensitivity analyses			
2.	Decrease by 10% on NIV	Equal between groups after 6 months (set NIV = IMV)	Equal between groups after 6 months (set NIV = IMV)
3.	Different between groups	Unequal between groups (carried forward)	Unequal between groups (carried forward)
4.	Different between groups	Unequal between groups (carried forward)	Equal between groups after 6 months (set NIV = IMV)

TABLE 35 Resource use by trial allocation, resource category and trial period for complete cases

Resource use category by time period	Trial group	
	Non-invasive weaning (*N* = 182)	Invasive weaning (*N* = 182)
Randomisation to hospital discharge		
Number of days in ICU [mean (SE)]	14.0 (1.078)	15.0 (1.12)
*Maximum number of organs supported [*n *(%)]*		
0	1 (< 1)	0
1	5 (3)	6 (3)
2	131 (72)	139 (76)
3	43 (24)	34 (19)
4	2 (1)	3 (2)
*Days in ICU for supporting [*n *(%)]*		
0 organs	7.0 (n/c)[a]	0
1 organ	12.8 (3.07)	8.0 (2.2)
2 organs	9.7 (0.64)	12.9 (0.7)
3 organs	18.1 (1.50)	13.1 (1.6)
4 organs	10.5 (3.50)	16.0 (7.4)
*Highest level of care [*n *(%)]*		
0/1	0	0
2	18 (10)	2 (1)
3	164 (9)	180 (99)
Days in ICU with highest level of care as: [mean (SE)]		
0/1	10.2 (0.78)	13.4 (1.06)
2	10.4 (0.83)	10.7 (0.74)
3	19.7 (2.15)	17.1 (1.78)
*Days in ICU with highest level of care as: [*n *(%)]*		
Tracheostomy	43 (24)	55 (30)
Antifungal use	10 (5)	21 (12)
Antiviral use	2 (1)	0
Emergency transport	37 (20)	39 (21)
Post discharge to 3 months (post randomisation) (3 months) *Inpatient care (hospital readmission) [mean (SE)* n *(%)]*	***Non-invasive weaning (N = 95)***	***Invasive weaning (N = 91)***
Length of stay (days)	2.8 (1.01) 19 (20)	6.0 (1.61) 22 (24)
Outpatient care (hospitals/clinics) [mean (SE) n *(%)]*		
Outpatient clinic (number of visits)	1.3 (0.20) 51 (54)	1.6 (0.30) 54 (59)
Radiology: MRI scan (number of visits)	0.1 (0.03) 4 (4)	0.0 (0.02) 4 (4)
Radiology: CT (number of visits)	0.1 (0.05) 7 (7)	0.1 (0.04) 10 (11)
Radiology: radiography (number of visits)	0.3 (0.09) 16 (17)	0.2 (0.05) 15 (17)
Radiology: ultrasonography (number of visits)	0.0 (0.02) 4 (4)	0.1 (0.03) 6 (7)
Hospital A&E (number of visits)	0.2 (0.05) 9 (10)	0.2 (0.06) 8 (9)
Other service: (number of visits)	1.1 (0.49) 24 (25)	0.8 (0.19) 26 (29)

TABLE 35 Resource use by trial allocation, resource category and trial period for complete cases (*continued*)

Resource use category by time period	Trial group	
	Non-invasive weaning (*N* = 182)	Invasive weaning (*N* = 182)
Residential care services [mean (SE) n *(%)]*		
Residential care home (number of days)	0.1 (0.08) 1 (1)	0.4 (0.24) 3 (3)
Rehabilitation centre (number of days)	0.7 (0.33) 5 (5)	1.6 (0.69) 6 (7)
Warden-controlled residence (number of days)	0.0 (0.00) 0 (0)	0.0 (0.00) 0 (0)
Day centre run by your local authority (number of days)	0.0 (0.00) 0 (0)	0.0 (0.00) 0 (0)
Other service (number of days)	0.5 (0.35) 4 (4)	0.2 (0.15) 2 (2)
Community health and social care [mean (SE) n *(%)]*		
GP surgery visit (number of visits)	2.1 (0.26) 59 (62)	1.9 (0.29) 58 (64)
GP home visit (number of visits)	0.3 (0.07) 19 (20)	0.5 (0.15) 20 (22)
GP telephone consultation (number of visits)	0.5 (0.12) 18 (19)	0.5 (0.13) 19 (21)
District nurse (number of visits)	3.5 (0.96) 33 (35)	3.7 (1.15) 29 (32)
Health visitor (number of visits)	0.0 (0.00) 0 (0)	0.0 (0.03) 2 (2)
Social worker (number of visits)	0.2 (0.11) 3 (3)	0.2 (0.05) 9 (10)
Physiotherapist (number of visits)	1.3 (0.41) 23 (24)	1.2 (0.29) 22 (24)
Occupational therapist (number of visits)	0.8 (0.29) 13 (14)	0.4 (0.10) 15 (16)
Counsellor (number of visits)	0.2 (0.14) 4 (4)	0.0 (0.04) 1 (1)
Psychologist (number of visits)	0.0 (0.02) 2 (2)	0.1 (0.07) 4 (4)
Home help/care worker (number of visits)	6.8 (2.40) 12 (13)	3.9 (2.10) 9 (10)
Other (number of visits)	2.2 (1.06) 18 (19)	2.2 (1.05) 19 (21)
Medication (on prescription)		
Number of medications [mean (SE) *n* (%)]	5.1 (0.46) 73 (77)	4.0 (0.39) 68 (75)
0 medications [*n* (%)]	17 (18)	22 (24)
1 medication [*n* (%)]	8 (8)	11 (12)
2 medications [*n* (%)]	9 (9)	4 (4)
3 medications [*n* (%)]	5 (5)	8 (9)
> 3 medications [*n* (%)]	51 (54)	45 (50)
Medication (over the counter)		
Number of medications [mean (SE) *n* (%)]	4.7 (1.11) 13 (14)	5.9 (1.36) 12 (13)
0 medications [*n* (%)]	78 (82)	81 (89)
1 medication [*n* (%)]	6 (6)	2 (2)
2 medications [*n* (%)]	0	0
3 medications [*n* (%)]	0	0
> 3 medications [*n* (%)]	7 (7)	8 (9)
Equipment and aids		
Patients who required equipment and aids [*n* (%)]	53 (56)	59 (65)

continued

TABLE 35 Resource use by trial allocation, resource category and trial period for complete cases (*continued*)

Resource use category by time period	Trial group	
	Non-invasive weaning (*N* = 182)	Invasive weaning (*N* = 182)
Provider, n *(%)*		
Health service/NHS	44 (46)	46 (51)
Patient	8 (8)	16 (18)
Charity	1 (1)	4 (4)
Social services	7 (7)	4 (4)
Other/not stated	1 (1)	2 (2)
Additional resource use by patient or partner/relative, n *(%)*		
Patients/partner/relative that used an additional resource	30 (32)	32 (35)
Travel cost incurred	19 (20)	25 (27)
Child care	1 (1)	1 (1)
Income lost	7 (7)	9 (10)
Housework	8 (8)	3 (3)
Laundry	4 (4)	3 (3)
Other	1 (1)	2 (2)
Post discharge 3 months to 6 months (post randomisation) (3 to 6 months) *Inpatient care (hospital readmission) [mean (SE)* n *(%)]*	***Non-invasive weaning (N = 93)***	***Invasive weaning (N = 84)***
Length of stay (days)/number of hospital visits	3.1 (1.26) 16 (17)	4.3 (2.19) 23 (27.4)
Outpatient care (hospitals/clinics) (number of visits) [mean (SE) n *(%)]*		
Outpatient clinic	1.9 (0.35) 49 (53)	1.5 (0.16) 61 (73)
Radiology: MRI scan	0.1 (0.05) 7 (8)	0.1 (0.04) 9 (11)
Radiology: CT	0.2 (0.06) 15 (16)	0.2 (0.04) 14 (17)
Radiology: radiography	0.2 (0.05) 12 (13)	0.2 (0.06) 12 (14)
Radiology: ultrasonography	0.1 (0.03) 6 (7)	0.1 (0.04) 11 (13)
Hospital A&E	0.1 (0.05) 7 (8)	0.2 (0.06) 10 (12)
Other service:	0.8 (0.30) 16 (17)	1.1 (0.45) 28 (33)
Residential care services (number of days) [mean (SE) n *(%)]*		
Residential care home	0.0 (0.00) 0 (0)	1.3 (1.02) 2 (2)
Rehabilitation centre	0.0 (0.00) 0 (0)	1.8 (1.23) 3 (4)
Warden-controlled residence	0.0 (0.00) 0 (0)	0.0 (0.00) 0 (0)
Day centre run by local authority	0.0 (0.00) 0 (0)	0.0 (0.01) 1 (1)
Other service	0.0 (0.00) 0 (0)	0.0 (0.00) 0 (0)
Community health and social care (number of visits) [mean (SE) n *(%)]*		
GP surgery visit	1.9 (0.34) 48 (52)	2.0 (0.23) 61 (73)
GP home visit	0.2 (0.06) 9 (10)	0.4 (0.14) 12 (14)
GP telephone consultation	0.4 (0.09) 20 (22)	0.2 (0.07) 13 (16)
District nurse	3.9 (1.66) 18 (19)	5.4 (2.16) 28 (33)
Health visitor	0.1 (0.05) 3 (3)	1.0 (0.98) 4 (5)
Social worker	0.0 (0.04) 2 (2)	0.2 (0.15) 4 (5)

TABLE 35 Resource use by trial allocation, resource category and trial period for complete cases (*continued*)

Resource use category by time period	Trial group	
	Non-invasive weaning (*N* = 182)	Invasive weaning (*N* = 182)
Physiotherapist	0.7 (0.24) 14 (15)	0.9 (0.37) 14 (17)
Occupational therapist	0.2 (0.15) 5 (5)	0.3 (0.14) 9 (11)
Counsellor	0.2 (0.16) 4 (4)	0.1 (0.04) 2 (2)
Psychologist	0.1 (0.04) 2 (2)	0.1 (0.04) 5 (6.0)
Home help/care worker	2.5 (1.43) 4 (4)	3.8 (2.35) 5 (6)
Other	1.1 (0.35) 13 (14)	1.5 (0.80) 16 (19)
Medication (on prescription)		
Number of medications [mean (SE) *n* (%)]	4.8 (0.46) 67 (72)	4.9 (0.50) 67 (80)
0 medications [*n* (%)]	15 (16)	25 (30)
1 medication [*n* (%)]	13 (14)	12 (14)
2 medications [*n* (%)]	5 (5)	2 (2)
3 medications [*n* (%)]	5 (5)	4 (5)
> 3 medications [*n* (%)]	44 (47)	49 (58)
Medication (over the counter)		
Number of medications [mean (SE) *n* (%)]	4.7 (1.11) 13 (14)	5.9 (1.36) 12 (14)
0 medications [*n* (%)]	74 (80)	80 (95)
1 medication [*n* (%)]	3 (3)	3 (4)
2 medications [*n* (%)]	0 (0)	1 (1)
3 medications [*n* (%)]	2 (2)	1 (1)
> 3 medications [*n* (%)]	3 (3)	7 (8)
Equipment and aids		
Patients who required equipment and aids [*n* (%)]	27 (29)	42 (50)
Provider, n *(%)*		
Health service/NHS	24 (26)	25 (30)
Patient	4 (4)	12 (14)
Charity	0 (0)	4 (5)
Social services	2 (2)	7 (8)
Other/not stated	2 (2)	4 (5)
Additional resource use by patient or partner/relative, n *(%)*		
Patients/partner/relative that used an additional resource	23 (25)	35 (42)
Travel cost incurred	19 (20)	23 (27)
Child care	0 (0)	0 (0)
Income lost	7 (8)	8 (10)
Housework	5 (5)	6 (7)
Laundry	4 (4)	4 (5)
Other	0 (0)	1 (1)

continued

TABLE 35 Resource use by trial allocation, resource category and trial period for complete cases (*continued*)

Resource use category by time period	Trial group	
	Non-invasive weaning (*N* = 182)	Invasive weaning (*N* = 182)
Post discharge to 6 months (post randomisation) (6 months) *Inpatient care (hospital readmission) [mean (SE)* n *(%)]*	***Non-invasive weaning*** **(N = *93*)**	***Invasive weaning*** **(N = *84*)**
Length of stay (days)/number of hospital visits	9.5 (2.45) 35 (38)	5.2 (1.52) 28 (33)
Outpatient care (hospitals/clinics) (number of visits) [mean (SE) n *(%)]*		
Outpatient clinic	2.9 (0.35) 77 (83)	2.8 (0.37) 71 (85)
Radiology: MRI scan	0.1 (0.04) 13 (14)	0.1 (0.05) 10 (12)
Radiology: CT	0.3 (0.06) 20 (22)	0.3 (0.08) 18 (21)
Radiology: radiography	0.3 (0.07) 25 (27)	0.4 (0.10) 23 (27)
Radiology: ultrasonography	0.2 (0.05) 15 (16)	0.1 (0.03) 10 (12)
Hospital A&E	0.3 (0.09) 15 (16)	0.2 (0.08) 14 (17)
Other service:	1.7 (0.44) 48 (52)	1.7 (0.52) 35 (42)
Residential care services (number of days) [mean (SE) n *(%)]*		
Residential care home	1.5 (0.99) 4 (4)	0.1 (0.07) 1 (1)
Rehabilitation centre	3.1 (1.27) 9 (10)	0.6 (0.31) 5 (6)
Warden-controlled residence	0.0 (0.00) 0 (0)	0.0 (0.00) 0 (0)
Day centre run by your local authority	0.0 (0.01) 1 (1)	0.0 (0.00) 0 (0)
Other service	0.2 (0.14) 2 (2)	0.5 (0.32) 4 (5)
Community health and social care (number of visits) [mean (SE) n *(%)]*		
GP surgery visit	3.5 (0.41) 76 (82)	3.5 (0.44) 77 (92)
GP home visit	0.8 (0.24) 23 (25)	0.4 (0.10) 24 (29)
GP telephone consultation	0.6 (0.15) 27 (29)	0.8 (0.14) 29 (35)
District nurse	8.4 (2.75) 46 (49)	6.6 (2.00) 42 (50)
Health visitor	1.0 (0.89) 6 (6)	0.1 (0.04) 3 (4)
Social worker	0.3 (0.16) 11 (12)	0.2 (0.12) 3 (4)
Physiotherapist	1.9 (0.44) 30 (32)	1.8 (0.46) 31 (37)
Occupational therapist	0.6 (0.16) 21 (23)	0.9 (0.34) 17 (20)
Counsellor	0.1 (0.06) 3 (3)	0.4 (0.25) 5 (6)
Psychologist	0.2 (0.09) 8 (9)	0.1 (0.06) 2 (2)
Home help/care worker	7.1 (2.98) 13 (14)	8.3 (2.95) 13 (15)
Other	3.4 (1.21) 28 (30)	2.9 (1.09) 24 (29)
Medication (on prescription)		
Number of medications [mean (SE) *n* (%)]	4.6 (0.849) 21 (23)	5.8 (0.953) 24 (29)
0 medications	61 (66)	68 (81)
1 medication	9 (10)	5 (6)
2 medications	0	3 (4)
3 medications	2 (2)	1 (1)
> 3 medications	10 (11)	15 (18)

TABLE 35 Resource use by trial allocation, resource category and trial period for complete cases (*continued*)

Resource use category by time period	Trial group	
	Non-invasive weaning (*N* = 182)	Invasive weaning (*N* = 182)
Medication (over the counter)		
Number of medications [mean (SE) *n* (%)]	4.6 (0.849) 21 (23)	5.8 (0.953) 24 (29)
0 medications	61 (66)	68 (81)
1 medication	9 (10)	5 (6)
2 medications	0	3 (4)
3 medications	2 (2)	1 (1)
> 3 medications	10 (11)	15 (18)
Equipment and aids		
Patients who required equipment and aids [*n* (%)]	70 (75)	61 (73)
Provider, n *(%)*		
Health service/NHS	54 (58)	54 (64)
Patient	24 (26)	10 (12)
Charity	6 (6)	1 (1)
Social services	10 (11)	7 (8)
Other/not stated	6 (6)	3 (4)
Additional resource use by patient or partner/relative, n *(%)*		
Patients/partner/relative that used an additional resource	46 (49)	41 (49)
Travel cost incurred	35 (38)	32 (38)
Child care	1 (1)	1 (1)
Income lost	11 (12)	10 (12)
Housework	7 (8)	10 (12)
Laundry	6 (6)	6 (7)
Other	3 (3)	1 (1)

A&E, accident and emergency; n/c, not calculable.
a The SE was not calculable because only one participant had a stay of 7 days in ICU.
Note
n indicates the number of participants who used a health resource at least once at a given assessment.
Patients with missing data at 3 months present with data at 6 months and patients with missing data at 6 months present with data at 3 months.

TABLE 36 Unit costs for resource items

Resource item	Unit cost (2015–16 prices)[a] (£)	Unit of analysis	Source
Intervention related			
Number of organs supported in the ICU (includes antimicrobial and sedative costs)			
0	759.00	Per day	NHS *Reference Costs 2016 to 2017*, Critical Care[59]
1	1031.00	Per day	NHS *Reference Costs 2016 to 2017*, Critical Care[59]
2	1399.00	Per day	NHS *Reference Costs 2016 to 2017*, Critical Care[59]
3	1619.00	Per day	NHS *Reference Costs 2016 to 2017*, Critical Care[59]
4	1794.00	Per day	NHS *Reference Costs 2016 to 2017*, Critical Care[59]
5	1977.00	Per day	NHS *Reference Costs 2016 to 2017*, Critical Care[59]
≥ 6	2274.00	Per day	NHS *Reference Costs 2016 to 2017*, Critical Care[59]
Highest level of care			
Level 3	1641.92		NICE – *Rehabilitation After Critical Illness* (CG83) 2009[60]
Level 2	1641.92		NICE – *Rehabilitation After Critical Illness* (CG83) 2009[60]
Level 1	303.65		*NHS Reference Costs 2013 to 2014*[61]
Tracheostomy	4151.51	Per procedure	*NHS Reference Costs 2014 to 2015*[36]
High-cost drugs			
Antibiotics			
Linezolid	0.074	Per mg	*Prescription Cost Analysis – England, 2016*[37]
Meropenem	0.016	Per mg	*Prescription Cost Analysis – England, 2016*[37]
Metronidazole	0.002	Per mg	*Prescription Cost Analysis – England, 2016*[37]
Antifungals			
Amphotericin Liposomal	1.644	Per mg	*Prescription Cost Analysis – England, 2016*[37]
Caspofungin	6.553	Per mg	*Prescription Cost Analysis – England, 2016*[37]
Voriconazole	0.197	Per mg	*Prescription Cost Analysis – England, 2016*[37]
Anidulafungin	3.000	Per mg	*Prescription Cost Analysis – England, 2016*[37]
Micafungin	3.41	Per mg	*Prescription Cost Analysis – England, 2016*[37]
Antiviral			
Abacavir	0.010	Per mg	*Prescription Cost Analysis – England, 2016*[37]
Atazanavir	0.034	Per mg	*Prescription Cost Analysis – England, 2016*[37]
Didanosine	0.013	Per mg	*Prescription Cost Analysis – England, 2016*[37]
Efavirenz	0.011	Per mg	*Prescription Cost Analysis – England, 2016*[37]
Emtricitabine	0.023	Per mg	*Prescription Cost Analysis – England, 2016*[37]
Enfuvirtide	10.02	Per mg	*Prescription Cost Analysis – England, 2016*[37]

TABLE 36 Unit costs for resource items (*continued*)

Resource item	Unit cost (2015–16 prices)[a] (£)	Unit of analysis	Source
Fesamprenavir	0.005	Per mg	*Prescription Cost Analysis – England, 2016*[37]
Idinavir	0.003	Per mg	*Prescription Cost Analysis – England, 2016*[37]
Lopinavir with Ritonavir	0.013	Per mg	*Prescription Cost Analysis – England, 2016*[37]
Navirapine	0.010	Per mg	*Prescription Cost Analysis – England, 2016*[37]
Ritonavir	0.006	Per mg	*Prescription Cost Analysis – England, 2016*[37]
Saquinavir	0.004	Per mg	*Prescription Cost Analysis – England, 2016*[37]
Stavudine	0.125	Per mg	*Prescription Cost Analysis – England, 2016*[37]
Tenofovir disoproxil	0.028	Per mg	*Prescription Cost Analysis – England, 2016*[37]
Zidovudine with lamivudine and Abacavir	0.024	Per mg	*Prescription Cost Analysis – England, 2016*[37]
Darunavir	0.012	Per mg	*Prescription Cost Analysis – England, 2016*[37]
Health resource use			
Inpatient care			
Cost per inpatient stay	173.56	Per bed-day	PSSRU – *Unit Costs of Health and Social Care 2010*,[62] p. 31
General medical ward	400.0	Per day	DHCS Communication (2015) https://data.gov.uk/data-request/nhs-hospital-stay (Department of Health and Social Care, March 2017, personal communication)
Outpatient care			
Outpatient clinic	115.52	Per visit	*NHS Reference Costs 2014 to 2015*[36]
MRI scan	170.74	Per test	*NHS Reference Costs 2013 to 2014*[36]
CT	94.06	Per test	*NHS Reference Costs 2013 to 2014*[36]
Radiography	27.60	Per test	*Portsmouth Clinical Commissioning Group*[63]
Ultrasonography	48.05	Per test	*NHS Reference Costs 2013 to 2014*[61]
Emergency department	133.76	Per session	*NHS Reference Costs 2014 to 2015*[36]
Emergency transport	£261.35	Per transfer	PSSRU – *Unit Costs of Health and Social Care 2011*[64]
Residential care			
Residential care home	151.63	Per day	PSSRU – *Unit Costs of Health and Social Care 2013*[38]
Rehabilitation centre	101.08	Per day	PSSRU – *Unit Costs of Health and Social Care 2013*[38]
Warden-controlled residence	63.06	Per day	PSSRU – *Unit Costs of Health and Social Care 2013*[38]
Local authority day centre	39.87	Per day	PSSRU – *Unit Costs of Health and Social Care 2013*[38]

continued

TABLE 36 Unit costs for resource items (*continued*)

Resource item	Unit cost (2015–16 prices)[a] (£)	Unit of analysis	Source
Community health and social care			
GP surgery	44.59	Per contact	PSSRU – *Unit Costs of Health and Social Care 2015*,[39] p. 177
GP home visit	138.35	Per home visit	PSSRU – *Unit Costs of Health and Social Care 2010*,[62] p. 167
GP telephone call	27.36	Per call	PSSRU – *Unit Costs of Health and Social Care 2015*,[39] p. 177
District nurse	38.51	Per contact	PSSRU – *Unit Costs of Health and Social Care 2015*,[39] p. 169
Health visitor	54.72	Per hour	PSSRU – *Unit Costs of Health and Social Care 2015*,[39] p. 169
Social worker	57.76	Per contact (average)	PSSRU – *Unit Costs of Health and Social Care 2015*,[39] p. 188
Community physiotherapist	49.02	Per contact	PSSRU – *Unit Costs of Health and Social Care 2013*[38]
Occupational therapist	74.63	Per contact (average)	PSSRU – *Unit Costs of Health and Social Care 2013*,[38] p. 176
Counsellor	49.07	Per hour	PSSRU – *Unit Costs of Health and Social Care 2013*,[38] p. 54
Community psychologist	60.32	Per hour	PSSRU – *Unit Costs of Health and Social Care 2013*[38]
Home help/care worker	24.32	Per hour	PSSRU – *Unit Costs of Health and Social Care 2015*,[39] p. 201
Medication			
Various medications	Range £0.01 – £271.88	Per dose	*Prescription Cost Analysis – England, 2016*[37]
Equipment and adaptations			
Various aids[b]	Range: 4.8 – 930.0	Per item	*National Catalogue* (2014–15)[41]

a Inflated to 2015–16 prices using *Unit Costs of Health and Social Care 2016*.[40]
b Equipment aids include support rails, bathroom aids and accessories, ramps, beds, wheelchairs and bed supports.

TABLE 37 Patient-reported EQ-5D-3L by trial allocation, trial period and dimension

	EQ-5D-3L dimension, *n* (%)															EQ VAS	Utility
	Mobility			Self care			Usual activities			Pain/discomfort			Anxiety/depression				
Time point	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3	Mean (SE)	Mean (SE)
Prior to hospital admission[a]																	
NIV (*N* = 122)	63 (52)	56 (46)	3 (2)	93 (76)	27 (22)	2 (2)	69 (57)	39 (32)	14 (11)	63 (52)	43 (35)	16 (13)	74 (61)	37 (30)	10 (8)	58.7 (1.98)	0.66 (0.031)
IMV (*N* = 120)	65 (54)	49 (41)	6 (5)	88 (73)	25 (21)	7 (6)	76 (63)	35 (29)	9 (8)	66 (55)	39 (33)	15 (13)	78 (65)	34 (28)	8 (7)	60.7 (2.01)	0.67 (0.033)
p-value[b]																0.491	0.733
3 months post ICU discharge																	
NIV (*N* = 91)	25 (27)	66 (71)	2 (2)	53 (58)	36 (40)	3 (3)	21 (23)	52 (57)	19 (21)	26 (29)	56 (62)	11 (12)	39 (43)	45 (49)	8 (9)	60.9 (2.03)	0.53 (0.035)
IMV (*N* = 88)	24 (27)	64 (71)	2 (2)	52 (59)	35 (40)	4 (5)	21 (24)	54 (61)	15 (17)	26 (30)	55 (63)	9 (10)	49 (56)	36 (41)	5 (6)	62.5 (2.11)	0.56 (0.035)
p-value[b]																0.593	0.543
6 months post ICU discharge																	
NIV (*N* = 91)	28 (31)	59 (65)	4 (4)	54 (59)	32 (35)	5 (5)	27 (30)	46 (51)	19 (21)	30 (33)	47 (52)	15 (16)	45 (49)	40 (44)	6 (7)	61.7 (2.35)	0.53 (0.032)
IMV (*N* = 82)	31 (38)	50 (61)	1 (1)	53 (65)	26 (32)	2 (2)	25 (30)	48 (59)	7 (9)	33 (40)	45 (55)	3 (4)	50 (61)	26 (32)	4 (5)	65.0 (2.34)	0.66 (0.039)
p-value[b]																0.377	0.0147

a These data were recollected using questionnaires administered at the point of discharge following the initial hospitalisation.
b Comparisons of EQ VAS and Utility score using student's *t*-test for unequal variances based on complete cases.

Note
Some categories have missing values (not included in percentage computation); for EQ VAS, n = 92 and 91 for NIV and IMV respectively at 3 months.

TABLE 38 Longer-term cost-effectiveness results and sensitivity analyses

Analyses	Incremental cost (£)	Incremental QALY	ICER	INMB[a] (£)	Probability of cost-effectiveness[a]
Base case (trial)	(302)	0.01589	NIV dominant	779	0.59
1. Assuming costs and utilities are equal between groups after 6 months[b]	2737	0.424	£4651	10,748	1.0
Sensitivity analyses					
2. Decrease in extrapolated survival rates in NIV group by 10%, equal costs and utilities carried forward[c]	237	0.028	£8393	603	0.96
3. Assuming costs and utilities are unequal between groups, costs and utilities carried forward[d]	6631	0.019	£349,000	(6061)	0.01
4. Assumes costs are equal between groups, but utilities carried forward[e]	2737	0.019	£144,052	(2167)	0.02

a Willingness to pay of £30,000.
b No further future differential benefits or costs assumed between treatments.
c Survival rates on NIV are lower by 10%; costs assumed equal between groups, but utilities carried forward.
d Future costs (after 6 months) assumed unequal between groups; utility and costs observed at 6 months in trial carried forward.
e Assumes no differential costs, but utilities carried forward differ between groups (because of projected survival patterns).

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