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AJ Gray, S Goodacre, DE Newby, MA Masson, F Sampson, S Dixon, S Crane, M Elliott and J Nicholl, on behalf of the 3CPO study investigators

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Abstract

A multicentre randomised controlled trial of the use of continuous positive airway pressure and non-invasive positive pressure ventilation in the early treatment of patients presenting to the emergency department with severe acute cardiogenic pulmonary oedema: the 3CPO trial

AJ Gray,[1*] S Goodacre,[2] DE Newby,[3] MA Masson,[1] F Sampson,[2] S Dixon,[2] S Crane,[4] M Elliott[5] and J Nicholl,[2] on behalf of the 3CPO study investigators

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Objectives: To determine whether non-invasive ventilation reduces mortality and whether there are important differences in outcome by treatment modality.
Design: Multicentre open prospective randomised controlled trial.
Setting: Patients presenting with severe acute cardiogenic pulmonary oedema in 26 emergency departments in the UK.
Participants: Inclusion criteria were age > 16 years, clinical diagnosis of acute cardiogenic pulmonary oedema, pulmonary oedema on chest radiograph, respiratory rate > 20 breaths per minute, and arterial hydrogen ion concentration > 45 nmol/l (pH < 7.35).
Interventions: Patients were randomised to standard oxygen therapy, continuous positive airway pressure (CPAP) (5–15 cmH_2O) or non-invasive positive pressure ventilation (NIPPV) (inspiratory pressure 8–20 cmH_2O, expiratory pressure 4–10 cmH_2O) on a 1:1:1 basis for a minimum of 2 hours.
Main outcome measures: The primary end point for the comparison between NIPPV or CPAP and standard therapy was 7-day mortality. The composite primary end point for the comparison of NIPPV and CPAP was 7-day mortality and tracheal intubation rate. Secondary end points were breathlessness, physiological variables, intubation rate, length of hospital stay and critical care admission rate. Economic evaluation took the form of a cost–utility analysis, taken from an NHS (and personal social services) perspective.
Results: In total, 1069 patients [mean age 78 (SD 10) years; 43% male] were recruited to standard therapy ($n = 367$), CPAP [$n = 346$; mean 10 (SD 4) cmH_2O] or NIPPV [$n = 356$; mean 14 (SD 5)/7 (SD 2) cmH_2O]. There was no difference in 7-day mortality for standard oxygen therapy (9.8%) and non-invasive ventilation (9.5%; $p = 0.87$). The combined end point of 7-day death and intubation rate was similar, irrespective of non-invasive ventilation modality (CPAP 11.7% versus NIPPV 11.1%; $p = 0.81$). Compared with standard therapy, non-invasive ventilation was associated with greater reductions (treatment difference, 95% confidence intervals) in breathlessness (visual analogue scale score 0.7, 0.2–1.3; $p = 0.008$) and heart rate (4/min, 1–6; $p = 0.004$) and improvement in acidosis (pH 0.03, 0.02–0.04; $p < 0.001$) and hypercapnia (0.7 kPa, 0.4–0.9; $p < 0.001$) at 1 hour. There were no treatment-related adverse events or differences in other secondary outcomes such as myocardial infarction rate, length of hospital stay, critical care admission rate and requirement for endotracheal intubation. Economic evaluation showed that mean costs and QALYs up to

6 months were £3023 and 0.202 for standard therapy, £3224 and 0.213 for CPAP, and £3208 and 0.210 for NIPPV. Modelling of lifetime costs and QALYs produced values of £15,764 and 1.597 for standard therapy, £17,525 and 1.841 for CPAP, and £17,021 and 1.707 for NIPPV. These results suggest that both CPAP and NIPPV accrue more QALYs but at higher cost than standard therapy. However, these estimates are subject to substantial uncertainty.

Conclusions: Non-invasive ventilatory support delivered by either CPAP or NIPPV safely provides earlier improvement and resolution of breathlessness, respiratory distress and metabolic abnormality. However, this does not translate into improved short- or longer-term survival. We recommend that CPAP or NIPPV should be considered as adjunctive therapy in patients with severe acute cardiogenic pulmonary oedema in the presence of severe respiratory distress or when there is a failure to improve with pharmacological therapy.

Trial registration: Current Controlled Trials ISRCTN07448447.

Contents

List of abbreviations

CPAP	continuous positive airway pressure
EPAP	expiratory positive airway pressure
EQ-5D	EuroQol 5 dimensions
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
IPAP	inspiratory positive airway pressure
MI	myocardial infarction
NICE	National Institute for Health and Clinical Excellence
NIPPV	non-invasive positive pressure ventilation
OR	odds ratio
PAS	patient administrative system
QALY	quality-adjusted life-year
WHO	World Health Organization

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

Non-invasive ventilation [continuous positive airway pressure (CPAP) or non-invasive positive pressure ventilation (NIPPV)] appears to be of benefit in the immediate treatment of patients with severe acute cardiogenic pulmonary oedema (patients with respiratory failure and distress) and may reduce mortality. Most published primary studies are small and patient populations, settings, severity of illness, interventions and outcomes vary considerably. None has been powered to detect a mortality difference as a primary outcome although meta-analyses suggest mortality benefit. Although there are mechanistic reasons for NIPPV to be superior to CPAP this has not been shown in the setting of a clinical trial.

Objectives

We aimed to determine whether non-invasive ventilation reduces mortality and whether there are important differences in outcome by treatment modality (CPAP or NIPPV).

Specifically we aimed to assess:

- the clinical effectiveness of non-invasive ventilation (CPAP or NIPPV) in addition to standard therapy against standard therapy alone in the early management of severe acute cardiogenic pulmonary oedema
- whether there is any difference in the effectiveness of CPAP and NIPPV in the early management of acute cardiogenic pulmonary oedema
- the safety of these interventions
- quality of life and patient satisfaction after treatment with non-invasive ventilation compared with standard therapy alone
- the incremental cost-effectiveness of non-invasive ventilation versus standard therapy from a health and social care perspective, in terms of cost per quality-adjusted life-year gained.

Design

In a multicentre open prospective randomised controlled trial, patients were randomised to one of three treatment arms: standard oxygen therapy, CPAP (5–15 cmH_2O) or NIPPV (inspiratory pressure 8–20 cmH_2O, expiratory pressure 4–10 cmH_2O). The two primary end points were 7-day mortality, and 7-day mortality or intubation rate.

Setting

Patients presenting with severe acute cardiogenic pulmonary oedema were recruited from 26 emergency departments in the UK.

Participants

Inclusion criteria were age > 16 years, clinical diagnosis of acute cardiogenic pulmonary oedema, pulmonary oedema on chest radiograph, respiratory rate > 20 breaths per minute, and arterial hydrogen ion concentration > 45 nmol/l (pH < 7.35).

Interventions

Eligible patients were consented and randomised using a telephone randomisation service to standard oxygen therapy, CPAP or NIPPV on a 1:1:1 basis. Other concomitant therapies were administered at the discretion of the treating clinician but the trial guideline advocated the use of nitrates. The interventions were for a minimum of 2 hours but the treating clinician was free to change the treatment if it was felt that it was clinically appropriate. Data collected included patient demographic, historical and physiological characteristics, intubation, mortality, diagnosis of myocardial infarction (MI), length of stay, critical care admission including length of stay, and patient symptoms measured by a dyspnoea scale. All

patients, if possible, were approached for repeat consent within 7 days of recruitment. The trial received multicentre research ethics committee approval (MREC/02/0/074) and was registered.

Repeat arterial blood gas analysis and Glasgow Coma Score were performed 1 hour after recruitment, and pulse, respiratory rate, oxygen saturation and non-invasive blood pressure were recorded at 1 and 2 hours. Patients completed a self-reported dyspnoea visual analogue scale [no breathlessness (0) to maximal breathlessness (10)] at recruitment and at 1 hour. A research nurse administered a patient satisfaction questionnaire within the following week. Patients were mailed a self-complete questionnaire at 1, 3 and 6 months after randomisation consisting of the EuroQol 5 dimensions (EQ-5D) health utility survey and a resource use questionnaire.

Main outcome measures

The primary end point for the comparison between non-invasive ventilation (NIPPV or CPAP) and standard oxygen therapy was 7-day mortality. The primary end point for the comparison of NIPPV and CPAP was a composite end point of 7-day mortality and tracheal intubation rate. A priori secondary end points were breathlessness, physiological variables, intubation rate, length of hospital stay and critical care admission rate.

Myocardial infarction was defined according to the 1971 World Health Organization (WHO) and the European Society of Cardiology/American College of Cardiology criteria. Two cardiologists blinded to treatment allocation assigned the following categories: definite MI, probable MI, possible MI and no MI. Incident cases of MI were defined as the composite of definite and probable MI.

The economic evaluation took the form of a cost–utility analysis, taken from an NHS (and personal social services) perspective, with outcomes measured in the form of quality-adjusted life-years (QALYs). Resources used by individual patients within the trial were quantified using data from the data collection form, the hospital patient administrative system and the resource use questionnaire. These were combined with unit costs to produce a total cost for each patient. Patient-level costs were then combined with patient-level EQ-5D data to produce an incremental cost per QALY and a probability that each treatment group is cost-effective at current funding levels.

Results

A total of 1069 patients [78 ± 10 years (mean ± SD); 43% male] were recruited to standard oxygen therapy ($n = 367$), CPAP [$n = 346$; 10 ± 4 cmH_2O (mean ± SD)] or NIPPV [$n = 356$; $14 \pm 5/7 \pm 2$ cmH_2O (mean ± SD)]. There was no difference in 7-day mortality for standard oxygen therapy (9.8%) and non-invasive ventilation (9.5%; $p = 0.87$). The combined end point of 7-day death or intubation rate was similar, irrespective of non-invasive ventilation modality (11.7% versus 11.1% for CPAP versus NIPPV respectively; $p = 0.81$). In comparison with standard oxygen therapy, non-invasive ventilation was associated with greater reductions (treatment difference, 95% confidence intervals) in breathlessness (visual analogue scale score 0.7, 0.2–1.3; $p = 0.008$) and heart rate (4/min, 1–6; $p = 0.004$) and improvement in acidosis (pH0.03, 0.02–0.04; $p < 0.001$) and hypercapnia (0.7 kPa, 0.4–0.9; $p < 0.001$) at 1 hour. There were no treatment-related adverse events. There were no differences in other secondary outcomes such as MI rate, length of hospital stay, critical care admission rate and requirement for endotracheal intubation.

Economic evaluation showed that mean costs and QALYs up to 6 months were £3023 and 0.202 for standard therapy, £3224 and 0.213 for CPAP, and £3208 and 0.210 for NIPPV. Modelling of lifetime costs and QALYs produced values of £15,764 and 1.597 for standard therapy, £17,525 and 1.841 for CPAP, and £17,021 and 1.707 for NIPPV. These results suggest that both CPAP and NIPPV accrue more QALYs but at higher cost than standard therapy. However, these estimates are subject to substantial uncertainty.

Conclusions

Non-invasive ventilatory support delivered by either CPAP or NIPPV safely provides earlier improvement and resolution of breathlessness, respiratory distress and metabolic abnormality. However, this does not translate into improved short- or longer-term survival. We recommend that non-invasive ventilation (CPAP or NIPPV) should be considered as adjunctive therapy in patients with severe acute cardiogenic pulmonary oedema in the presence of severe respiratory distress or when there is a failure to improve with pharmacological therapy.

Further research needs to address whether certain subgroups of patients may specifically benefit

from early application of non-invasive ventilation, for example patients with co-existent chronic obstructive pulmonary disease or particular underlying pathophysiological processes of pulmonary oedema (hypertensive heart failure).

Trial registration

This trial is registered as ISRCTN07448447.

Chapter 1
Introduction

Background

Acute cardiogenic pulmonary oedema is a common medical emergency and accounts for an estimated 15,000–20,000 acute hospital admissions per annum in the UK. Decompensated heart failure is one of the leading causes of hospitalisation in the USA where it accounts for 6.5 million hospital days each year;[1] it is now the leading reason for hospital admission in patients over 65 years.[2] It is associated with a high (5–15%) in-hospital mortality rate,[3,4] especially when secondary to acute myocardial infarction (MI)[5] or requiring critical care.[6] Conventional treatments include oxygen, diuretic, opioid and vasodilator therapy. Patients who fail to respond to such treatment have traditionally required intubation and ventilation with the associated potential complications.[7–9]

More recently it has been suggested that non-invasive ventilation may reduce the requirement for endotracheal intubation and mechanical ventilation and improve patient physiology. Although no single trial has been powered for mortality as its primary outcome, recent meta-analyses[10–16] suggest that there is a mortality benefit.

Non-invasive ventilation – mechanism of action

Non-invasive ventilatory support can avoid the need for tracheal intubation by improving oxygenation, reducing the work of breathing and increasing cardiac output.[17–20] Two common methods employ continuous positive airway pressure (CPAP) or non-invasive positive pressure ventilation (NIPPV) through a facial mask. CPAP maintains the same positive pressure support throughout the respiratory cycle whereas NIPPV increases airway pressure more during inspiration than during expiration. In comparison with CPAP, NIPPV gives greater improvements in oxygenation and carbon dioxide clearance, and a bigger reduction in the work of breathing. Because of this differential between inspiration and expiration a higher mean pressure can be tolerated and maintained, although this may lead to potentially harmful falls in blood pressure.[21] It is therefore unclear whether NIPPV is superior to CPAP in the treatment of cardiogenic pulmonary oedema.

Previous trial findings

There has been a steady stream of published randomised trials investigating the effectiveness of non-invasive ventilation in the management of severe acute cardiogenic pulmonary oedema in the last 20 years.[21–36] None has been powered to detect mortality benefit as the primary outcome and most have used a variety of surrogate end points such as physiological parameters, intubation or predefined treatment failure. Moreover, these trials have investigated the comparative effectiveness of CPAP versus standard oxygen therapy,[22–27] NIPPV versus standard oxygen therapy,[28–30] NIPPV versus CPAP[21,31–33] or either intervention (CPAP and NIPPV) versus standard oxygen therapy alone.[34–36] Almost all of these trials, now numbering approximately 25, have shown that non-invasive ventilation improves physiological variables, endotracheal intubation rates or other surrogate markers of treatment failure.

One study by Mehta and colleagues[21] was terminated prematurely because of an excess number of patients with acute MI in the NIPPV arm. Other studies specifically designed to address this issue have not confirmed any relationship between NIPPV and MI rate.[31]

Despite the lack of definitive mortality benefit, non-invasive ventilation is increasingly being used in clinical practice[37] and advocated by a number of specialty organisations.[38–40] In an attempt to determine whether a true mortality benefit exists, a number of authors have reviewed and assimilated relevant data and published systematic reviews with meta-analyses.[10–16,41,42] The following section reviews the key meta-analyses and recent primary trials.

Recent systematic reviews with meta-analyses

There have been seven systematic reviews published since 2005,[10–16] all reporting comparable findings and drawing broadly similar conclusions.

Masip and colleagues[10] identified 15 eligible randomised controlled trials comparing non-invasive ventilation with standard oxygen or with another type of non-invasive ventilation, i.e. CPAP compared with NIPPV. Data from studies were extracted on to a standardised data collection form by two independent reviewers and checked by a third. Methodological quality was assessed by a recognised scoring system.[43] The primary outcomes for the systematic review were in-hospital mortality and treatment failure as all included trials reported these outcomes. Treatment failure was inconsistently categorised and the authors defined this arbitrarily as the 'need to intubate'. Data on MI rates during hospital admission were collected and analysed. All other parameters such as physiological variables, length of stay and critical care admission were not consistently reported across trials. There were six trials comparing only CPAP with standard oxygen therapy, three comparing only NIPPV with standard oxygen therapy, three trials with three trial arms (two interventions CPAP or NIPPV) and three studies comparing CPAP with NIPPV. The majority of trials were single centre,[21–26,29–32,34,35] based in an intensive care unit (ICU)[22–25,29] or emergency department[21,26–28,30–36] or both,[22] took place in 10 different countries and included small numbers of patients (sample size 26–130). The majority used full face masks, and CPAP (2.5–16 cmH_2O) and NIPPV (8/3 to 20/5 cmH_2O) levels varied. There was considerable variation in the complexity of ventilator design. Only one study[27] used mortality as a primary end point. In general, methodological quality of the included trials was adequate. *Figures 1* and *2* detail the principal data synthesis for the review's primary comparisons.[10] There were data on 727 patients for the comparison of non-invasive ventilation (CPAP or NIPPV) with standard oxygen. Patients receiving non-invasive

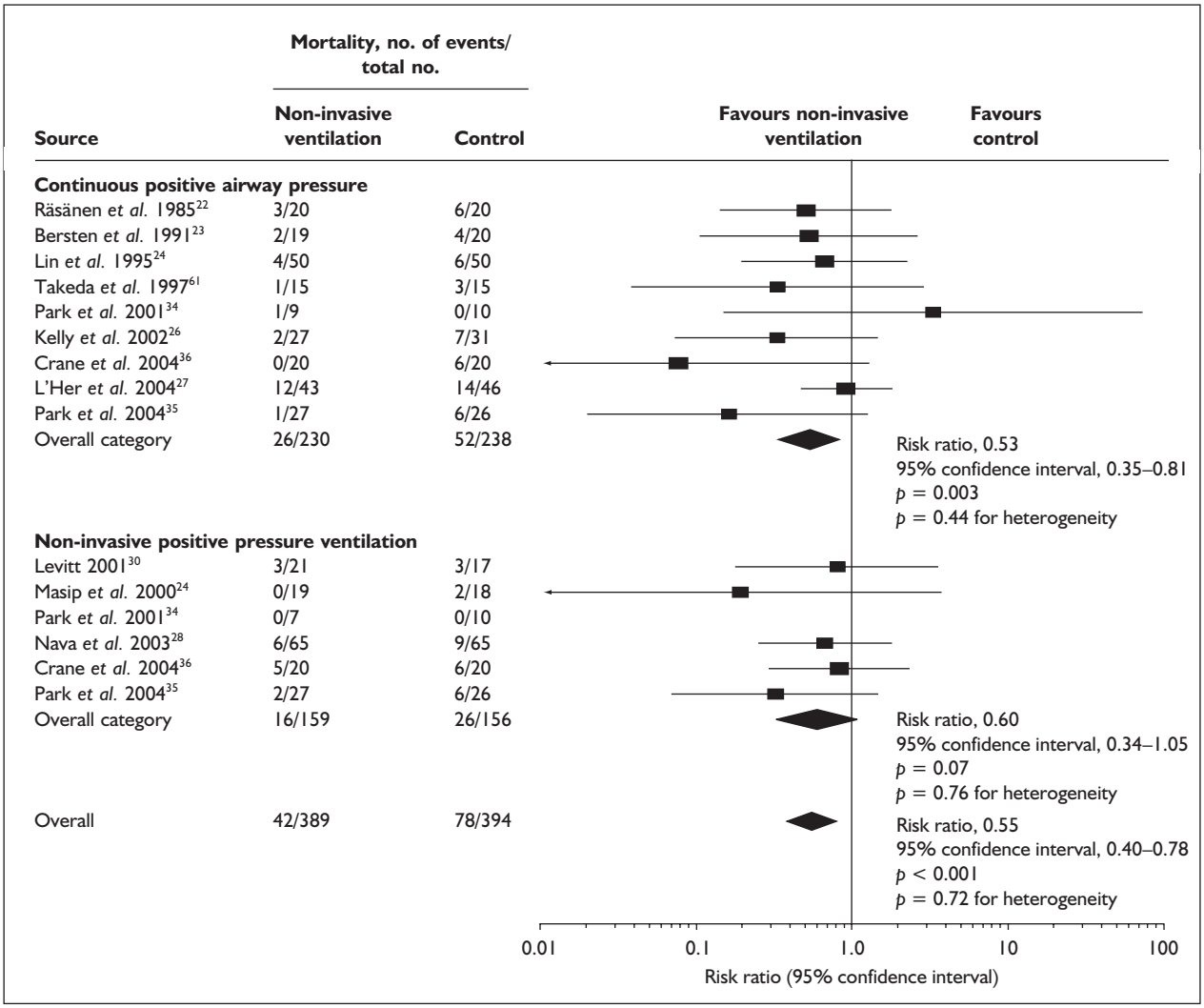

FIGURE 1 *Pooled data – non-invasive ventilation compared with standard oxygen therapy: outcome of in-hospital mortality. Adapted from Masip et al.,[10] with permission of the American Medical Association.*

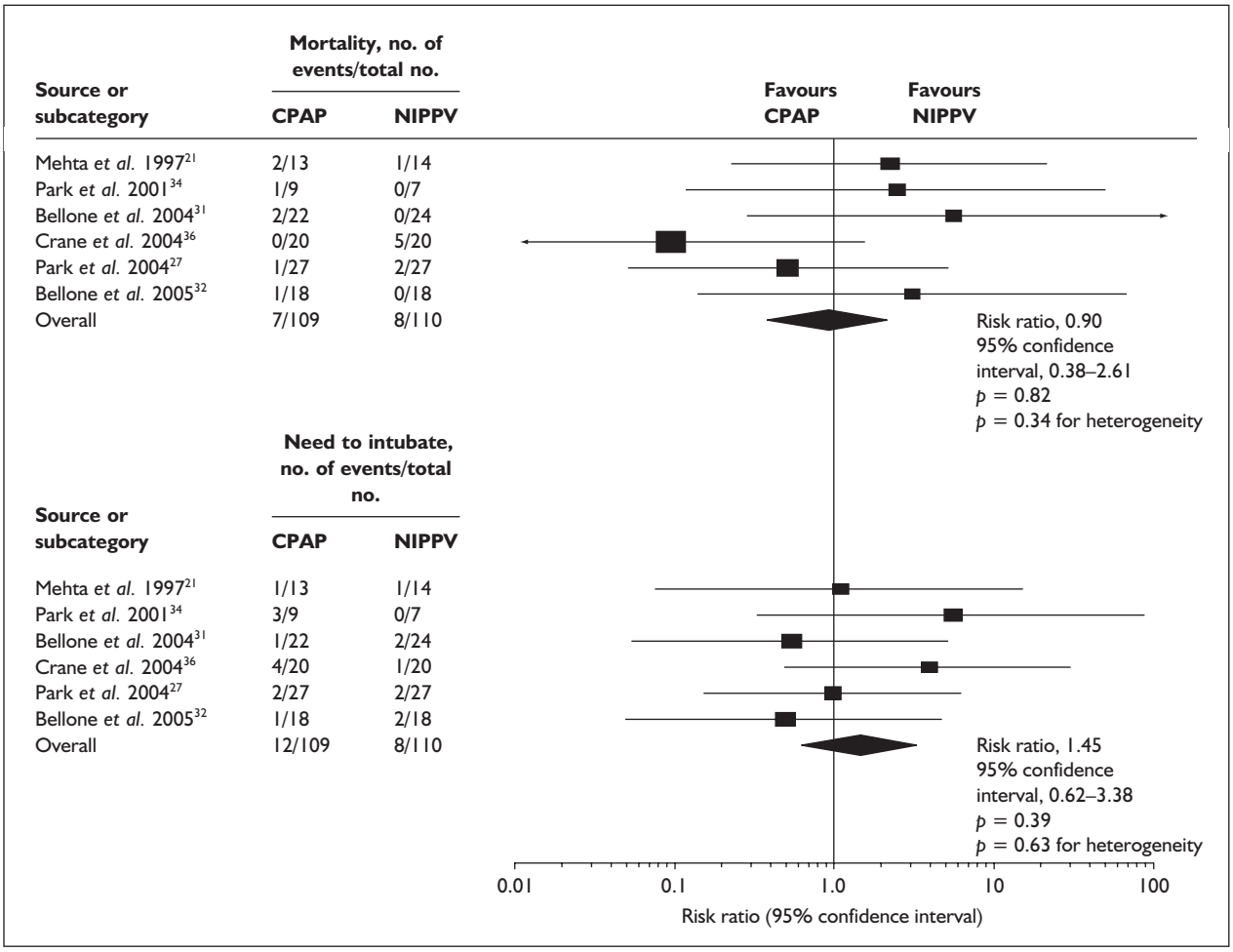

FIGURE 2 *Pooled data – CPAP compared with NIPPV: outcomes of in-hospital mortality and endotracheal intubation. Adapted from Masip et al.,[10] with permission of the American Medical Association. © 2005 American Medical Association. All rights reserved.*

ventilation had a reduction in in-hospital mortality (risk ratio 0.55, 95% CI 0.40–0.78; $p < 0.01$) and endotracheal intubation (risk ratio 0.48, 95% CI 0.32–0.57; $p < 0.01$). Results remained significant if CPAP was analysed independently for both in-hospital mortality and need for intubation. NIPPV comparisons are limited by the relatively smaller number of trial participants ($n = 315$) but it appeared to reduce mortality ($p = 0.07$) and intubation rates ($p = 0.02$). There was no difference in outcomes between CPAP and NIPPV but these comparisons included a total of only 219 patients. There was no difference in MI rates between arms. Tests for heterogeneity and publication bias were not significant. Masip and colleagues[10] concluded that this meta-analysis demonstrated improved survival in patients receiving non-invasive ventilation and that this should be considered first-line therapy in patients presenting with acute cardiogenic pulmonary oedema.

In a further meta-analysis Peter and colleagues[11] identified 23 eligible studies from 14 countries over an 18-year period. Data assimilation of these trials, including eight not included in the review by Masip and colleagues,[10] resulted in similar findings. Once again the design of the systematic review was of a high standard. The primary outcomes chosen were in-hospital mortality and need for intubation and mechanical ventilation. Secondary outcomes included treatment failure, length of hospital stay, length of time that non-invasive ventilation was applied and MI rate. There was a reduction in mortality for those patients treated with CPAP (relative risk 0.59, 95% CI 0.28–0.90; $p = 0.015$; number needed to treat, 5). There was a trend towards improved survival with NIPPV. Both CPAP (relative risk 0.44, 95% CI 0.29–0.66; $p = 0.0003$; number needed to treat, 6) and NIPPV (relative risk 0.50, 95% CI 0.27–0.90; $p = 0.02$; number needed to treat, 7) showed benefit when intubation

was an outcome. There was no difference in any outcome when CPAP and NIPPV were compared. There was a trend towards an increase in MI rate with NIPPV but this was largely caused by the weighting of the study by Mehta and colleagues.[21] Peter and colleagues[11] suggested that both therapies are effective although, because of the relatively small proportions of pulmonary oedema patients included in these trials, their results are difficult to generalise.[11] In addition it was felt that further work was required to better define the relationship between positive end-expiratory pressure and myocardial ischaemia, as well as further trials in hypercapnic patients with acute cardiogenic pulmonary oedema.

These meta-analyses[10–16] were published after the trial commenced and were therefore provided to the trial steering committee and data monitoring committee. Both were felt not to materially change the need for a large adequately powered randomised controlled trial investigating the overall effectiveness of non-invasive ventilation and the comparable effectiveness of NIPPV and CPAP.

Trial aims and objectives

Aims

In patients with severe acute cardiogenic pulmonary oedema, studies of non-invasive ventilation have consistently demonstrated an early improvement in physiological variables including arterial oxygenation and heart and respiratory rate. However, because of small sample sizes, the benefits of non-invasive ventilation for clinical outcomes such as intubation rate and mortality remain unproven. A large multicentre trial was therefore required to establish whether:

1. Non-invasive ventilation reduces mortality when compared with standard therapy.
2. NIPPV is more effective than CPAP.
3. The rate of MI is increased by non-invasive ventilation.

Principal objectives

In this multicentre randomised controlled trial of non-invasive ventilation in the early management of patients with severe acute cardiogenic pulmonary oedema (the 3CPO trial) we wished to determine:

1. the clinical effectiveness of non-invasive ventilation (CPAP or NIPPV) in addition to standard therapy against standard therapy alone
2. the comparative effectiveness of CPAP and NIPPV
3. the safety of non-invasive ventilation
4. patient satisfaction after treatment with non-invasive ventilation compared with standard therapy alone
5. the 6-month survival and quality of life of patients presenting with severe acute cardiogenic pulmonary oedema
6. the incremental cost-effectiveness of non-invasive ventilation versus standard therapy from a health and social care perspective, in terms of cost per quality-adjusted life-year (QALY) gained.

Chapter 2
Methods

Overview

This study was an open prospective randomised controlled trial comparing two intervention arms (CPAP and NIPPV) with standard oxygen therapy alone in patients presenting with severe acute cardiogenic pulmonary oedema. Patients were recruited on a 1:1:1 basis to standard oxygen therapy, CPAP or NIPPV. The intervention was delivered for a minimum of 2 hours.

Participants

Inclusion criteria

- Patients older than 16 years of age.
- Signs and symptoms consistent with acute cardiogenic pulmonary oedema as the principal clinical complaint: acute dyspnoea and bilateral crackles on chest auscultation.
- Chest radiograph confirming the diagnosis of acute cardiogenic pulmonary oedema: typical features of interstitial oedema present.
- Arterial blood gas analysis with a pH of < 7.35 (hydrogen ion concentration > 45 nmol/l).
- Respiratory rate of > 20 breaths per minute.

Exclusion criteria

- Severely altered consciousness (unconscious or responding to pain only).
- Any patient requiring an immediate lifesaving intervention, such as cardiopulmonary resuscitation, airway control, cardioversion or inotropic support.
- Any patient requiring thrombolysis or percutaneous coronary intervention for acute ST-segment elevation myocardial infarction.
- A clear alternative primary diagnosis, such as lobar pneumonia.
- An inability to provide informed consent at any time within the trial period, such as dementia or other form of incapacity.
- Previous inclusion in the 3CPO study.

Interventions

All randomised patients received a minimum of 2 hours of their allocated treatment. Other therapies were at the discretion of the treating clinical team.

A pragmatic decision was made to use a midrange ventilator that was able to deliver both types of ventilation (CPAP and NIPPV). The BiPAP® Synchrony® [Respironics (UK), Chichester] is a compact portable ventilator used to deliver the non-invasive intervention. Up to 15 l/min of oxygen can be entrained into the face mask, delivering a maximum oxygen concentration of 60% depending on an individual patient's tidal volume and mask leak.

Standard oxygen therapy

Patients randomised to standard medical therapy received supplemental oxygen via a variable delivery oxygen mask with a reservoir to maintain saturations above 92%.

Continuous positive airway pressure

Patients randomised to CPAP were fitted with a self-sealing full face mask connected to the BiPAP Synchrony ventilator set to CPAP function at a starting pressure of 5 cmH_2O. Oxygen was entrained into the system at 15 l/min and subsequently adjusted to maintain oxygen saturation above 92%. CPAP pressure was titrated in 2-cmH_2O steps at 2- to 3-minute intervals over the first 10–15 minutes to a maximum pressure of 15 cmH_2O according to the clinical response and tolerance of the patient.

Non-invasive positive pressure ventilation

Patients randomised to NIPPV were fitted with a self-sealing full face mask connected to the BiPAP

Synchrony ventilator set to NIPPV ventilation in spontaneous/timed mode with a backup respiratory rate of 12 breaths/min. The starting inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) are preset to 8 cmH_2O and 4 cmH_2O respectively. Oxygen was entrained into the system at 15 l/min and subsequently adjusted to maintain oxygen saturation above 92%. IPAP and EPAP were titrated at 2- to 3-minute intervals over the first 15–18 minutes to maximum pressures of 20 cmH_2O and 10 cmH_2O, respectively, according to the clinical response and tolerance of the patient. IPAP is increased by 2-cmH_2O and EPAP by 1-cmH_2O increments.

Additional therapy

All groups received standard therapy at the discretion of the attending physician. All centres were encouraged to use nitrate (buccal or intravenous) therapy. All other therapy, including intravenous loop diuretic and opioid therapy, was documented. A trial treatment guideline was developed and readily available in all recruiting emergency departments (see Appendix 1).

Failure of allocated treatment

There were no prespecified criteria for treatment failure. Clinicians were free to make the decision to stop an allocated treatment and to cross over to an alternative treatment including endotracheal intubation and mechanical ventilation. Crossovers were documented and analysed as secondary end points (see *Table 1*).

Outcome measures

Primary end points

The primary end point for the comparison of non-invasive ventilation (CPAP and NIPPV) with standard therapy was 7-day mortality. The primary end point for the comparison of CPAP with NIPPV was the composite of 7-day mortality and intubation.

Secondary end points

Based on data from our pilot studies,[26,36] the rapidity and efficacy of response to treatment was assessed using several secondary end points. These include symptoms, tolerability, side effects and physiological variables (*Table 1*). In addition, cost-effectiveness was determined by assessing the use of health-care resources, quality of life and long-term survival.

Definition of myocardial infarction

Two consultant cardiologists blinded to treatment allocation adjudicated on the diagnosis of MI in the following categories: definite MI, probable MI, possible MI and definite no MI. Incident cases of MI were defined as the composite of definite and probable MI.

Because of the transition in definitions at trial outset, the diagnosis of MI was defined according to both the 1971 World Health Organization (WHO) and the 2000 European Society of Cardiology/American College of Cardiology criteria.[44] The effect of the intervention was assessed against the rate of MI as defined by both criteria.

Patient satisfaction

Patient satisfaction with the treatment in the emergency department was determined using a questionnaire consisting of the outcomes and attitudes towards care questions from the widely used Group Health Association of America (GHAA) consumer satisfaction survey.[45] This was ideally self-completed, although the research team assisted in the completion if requested when they visited the patient in the first week after recruitment.

Sample size

The trial addresses two distinct questions:

1. Is non-invasive ventilation superior to standard oxygen therapy?
2. Which form of non-invasive ventilation is the most efficacious: CPAP or NIPPV?

To maximise the ability to address these two distinct questions in the three groups we aimed to recruit 400 patients to each allocated treatment.

Is non-invasive ventilation superior to standard oxygen therapy?

The primary end point was 7-day mortality. Seven previous studies of acute cardiogenic pulmonary oedema[22–26,29,36] (n = 11–50 per treatment group) at the time of protocol development had assessed standard facial oxygen therapy in comparison with

TABLE 1 *Secondary end points*

Physiology	Arterial blood analysis	Hydrogen ion concentration/pH
		Partial pressure of oxygen
		Partial pressure of carbon dioxide
	Pulse oximetry	Oxygen saturation
	Respiratory rate	Breaths per minute
	Blood pressure	Systolic, diastolic and mean
	Heart rate	Rate per minute
Symptoms	Dyspnoea	Patient-assessed breathlessness score
	Tolerability	
	Side effects	Gastric dilatation, facial abrasions
Adverse events		Myocardial infarction
Treatment failure		Worsening acidosis, hypercapnia or hypoxemia after 1 hour
		Progressive respiratory distress
		Inability to tolerate allocated treatment
Patient satisfaction		

CPAP ventilation, with only two further available studies[29,34] assessing NIPPV ventilation. The pooled data showed a mortality rate of 21% (38/181) in patients receiving standard facial oxygen and 9% (16/173) in those receiving CPAP ventilation.

In this trial we aimed to be able to detect a 6% absolute difference in mortality, which is half the effect size previously reported.[41] To have an 80% chance of detecting a 6% difference (9% versus 15%) using a two-sided significance level of 0.05 we needed approximately 400 patients randomised to standard facial oxygen therapy and 800 patients randomised to either CPAP or NIPPV.

Which form of non-invasive ventilation is the most efficacious?

It is possible that the treatment effect between the two modes of non-invasive ventilation will be smaller than that observed compared with standard oxygen therapy. To help draw out any plausible and clinically useful treatment effects the additional primary end point of a composite of 7-day mortality and intubation rate was included.

With 400 patients in each of the CPAP and NIPPV arms the trial aimed to have 80% power using a two-sided significance level of 0.05 to detect an absolute difference of approximately 7% in the composite end point (18% versus 11%) and of approximately 6% in mortality (12% versus 6%).

Patient consent processes

Informing participants of benefits and risks

Patients were given an information sheet (Appendix 2) to read before consent was obtained. Those patients who were severely unwell were given the risks and benefits of participation in the trial verbally. In these cases the fact that the information had been given verbally and understood by the patient was witnessed and the information sheet left with the patient to read later. Patients' relatives were also given an information sheet at the time of patient consent or relative assent (Appendix 3).

Obtaining consent or assent

Written informed consent was obtained before randomisation whenever possible (Appendix 4). When a patient was unable to give written consent, either witnessed verbal consent or relatives' assent was obtained (Appendix 5). Verbal patient consent was witnessed in writing by a second individual involved in the patient's clinical care. Subsequent written consent was obtained as soon as possible prior to the patient's data being used in the trial and normally within 1 week of recruitment (Appendices 6 and 7).

In the event of a patient being unable to give informed written or verbal consent, and when there was no accompanying relative who was willing

to give assent, the patient was excluded from the study and treated according to the emergency department's usual clinical practice.

Recruitment and randomisation

On arrival at the emergency department, attending medical and nursing staff recruited, consented and randomised patients meeting the entry criteria. Trial number and treatment allocation were performed by telephone contact to a central automated randomisation centre at the University of Leeds. Patients were randomised on a 1:1:1 basis to one of the three treatment options: CPAP, NIPPV or standard oxygen therapy. The randomisation sequence was generated by an independent statistician at the Leeds Clinical Trials Unit and stratified by centre with variable randomisation block length.

Statistical methods

Primary outcomes

The trial statistician, Professor Jon Nicholl, performed the primary statistical analyses. All outcomes were assessed by intention to treat analysis. The analysis first compared patient and clinical characteristics of the three randomised groups to identify any statistically important imbalances in the randomisation. Second, it compared mortality in the three arms using a logistic regression model with the degrees of freedom for differences between the three treatments decomposed into the two orthogonal contrasts of (1) standard therapy versus non-invasive ventilatory support (CPAP and NIPPV) and (2) CPAP versus NIPPV. Third, if appropriate, it compared mortality taking into account any statistically important imbalances. The analysis then compared the composite end point of death or intubation using the same statistical approach. Data were analysed using SPSS version 15.0. Mean and standard deviation were reported for most continuous variables unless inspection revealed skewed data, in which case median and interquartile range were reported. To compare means in two-group comparisons of continuous variables *t*-tests were used, and to compare means across all three study groups one-way analysis of variance was used. Chi-squared tests were used to compare categorical variables apart from the principal analyses outlined above.

Secondary outcomes

Data for the secondary end points, such as rate of MI, patient satisfaction (Appendix 8) and QALYs, admission to a high dependency area, length of stay and changes in physiology over the first 2 hours of treatment, were examined using analysis of variance-type models, with repeated measures and adjustment for baseline covariates as appropriate. Statistical significance was taken at the 5% level.

Prespecified subgroup analysis

It is possible that non-invasive ventilation could be more effective in patients with more severe illness who have a higher risk of death. We therefore planned to examine whether there was any interaction between illness severity and the effect of treatment with non-invasive ventilation upon the primary outcome (7-day mortality). Illness severity was defined a priori by the baseline pH and post hoc by the baseline physiological variable shown to have the strongest independent association with 7-day mortality. Analysis used logistic regression to determine the significance of any interaction between severity and treatment effect with 7-day mortality as the outcome.

Health economics

Health economic outcomes

The economic evaluation followed the methods used within the National Institute for Health and Clinical Excellence (NICE) Technology Appraisal Programme.[46] In summary, it took the form of a cost–utility analysis with outcomes measured in the form of QALYs based on utilities derived from patient-completed EuroQol 5 dimensions (EQ-5D) questionnaires. The perspective taken was that of the NHS (and personal social services). Prices were at 2005/6 levels.

The general approach adopted within the economic evaluation was to quantify the resources used by individual patients within the trial using appropriate data sources and then combine these with unit costs to produce a total cost for each patient. These patient-level costs were then combined with patient-level EQ-5D data to produce an incremental cost per QALY and a probability that each treatment group is cost-effective at current funding levels.

Whereas the primary focus of the clinical study was a comparison of non-invasive ventilation versus no non-invasive ventilation, the economic evaluation focused on a comparison of the three study groups. Another deviation from the clinical analysis was that two time frames were adopted within the economic evaluation, one reflecting the trial itself (up to 6 months post randomisation) and another reflecting the length of time over which relevant costs and outcomes are apparent (over the remaining lifetime of patients). It is the lifetime cost-effectiveness that is the primary economic analysis.

Data collection – economic analysis

Data for the economic evaluation were collected from three sources:

1. Hospital patient administrative systems (PAS) were searched to identify length of hospital stay in each location (ward, coronary care, high dependency unit and intensive care unit).
2. A postal questionnaire consisting of the EQ-5D health utility survey and a health and social care resource use survey was sent to every surviving patient at 1, 3 and 6 months with two remailings 2 weeks apart. The resource use questionnaire contained information on use of outpatient, primary, community and social care services (e.g. GP contacts, emergency department attendances) and prescriptions.
3. It was not practicable to collect detailed resource use information relating to the emergency department episode for all patients and so a subsample of trial patients was used as the basis for a microcosting study.

Measurement and valuation of outcomes

The EQ-5D data were combined to produce an area under the curve with respect to time measured in years to produce QALYs. The area was calculated as the sum of the three trapeziums defined by baseline utility (which is assumed to be zero) at 1 month, 3 months and 6 months. Patients who died had by definition a utility of zero from the point of death onwards. For the purposes of analysis, the time of death was operationalised as being at the previous point of data collection (i.e. 0, 1 or 3 months). So, for example, someone dying before the 1-month follow-up was assumed to produce zero QALYs. The same approach was used for those costs collected via the postal questionnaire; however, hospitalisation costs do not suffer from this problem.

Measurement and valuation of costs

Resources used by each patient measured from PAS and the resource use questionnaire were multiplied by national unit costs (see tables in Chapter 3) to generate an estimate of the overall cost per patient. The microcosting identified consecutive patients over approximately 6 months at three of the participating hospitals: Edinburgh, York and Sheffield. The research nurse and recruiting doctor retrospectively estimated the total time that each member of staff spent involved in patient care up to 2 hours after randomisation. The research nurse then recorded all diagnostic tests performed in the 2 hours after randomisation using case notes and computer records. In total, 68 patients were included in the study, with approximately the same number in each arm of the study. Resource use was then combined with unit costs plus overheads and an estimate of the cost per patient for providing CPAP and NIPPV. For CPAP and NIPPV the equivalent annual cost of a Respironics Synchrony ST ventilator was calculated as the sum of the purchase price, consumables and maintenance based on a 5-year life expectancy and a 3.5% discount rate payable in advance. The cost per patient was based on the equivalent annual cost and an estimated annual workload of 130.

Analysis

Calculation of costs and QALYs

Although complete data for hospitalisations cover the full 6 months of the trial, the questionnaire data relate only to 'the previous month'. Consequently, for those resources that are identified from the questionnaires, we do not know the level of use for month 2 and months 4–5. Resource use in these months is therefore estimated through linear interpolation of the preceding and following observations. Such an approach is in line with the calculation of QALYs.

Economic end points

The focus of the economic evaluation was the incremental cost per QALY ratios (also known as incremental cost-effectiveness ratios or ICERs) of the two more effective treatments, and the probability that each treatment (including the

control group) would be cost-effective. When evaluating these probabilities it is necessary to specify the monetary value of a QALY gain. This QALY value reflects a threshold, with interventions that generate QALYs at a cost which is below this value being deemed cost-effective.

Within England and Wales, NICE uses two QALY values when assessing cost-effectiveness: £20,000 and £30,000 per QALY. If a technology produces an ICER that is less than the lower valuation it is likely to be funded. Above this value a technology needs to demonstrate other characteristics that are of importance in order to be considered cost-effective. Above £30,000 per QALY there must be very strong auxilliary reasons for an intervention to be funded. Consequently, the economic evaluation reported here aims to produce the probabilities that each treatment is cost-effective at £20,000 and £30,000 per QALY. This will be reported in tandem with cost-effectiveness acceptability curves defined over the range £0–50,000 per QALY.

Comparisons of mean costs and QALYs were also undertaken using analysis of variance. Although it is unlikely that the underlying data for these comparisons are normally distributed, typically with costs being skew and QALYs generated from the EQ-5D being bimodal, the large sample sizes are thought to reduce the problems caused by using parametric tests.[47]

Missing data

The use of patient-reported outcomes and resource use typically produces rates of missing data of around 50% at 6 months for this patient population. Although this can lead to a bias in observed differences, there is no consensus on whether and how missing data should be imputed (and its role in the interpretation of a study's overall results). The primary analysis was a complete case analysis (i.e. using only patients with complete data at all time points), with an additional analysis undertaken using the last observation carried forward as a method of imputing missing data. When a preceding value was not available to be carried forward the next observation was carried backwards, and when no observation was available for a patient the group-specific mean value for living patients was used.

Time frame

The consequences of treatment potentially last for the lifetime of the patients and so the most relevant time frame is the remaining lifetime of patients. This formed the basis of the primary analysis. However, the costs and outcomes for such an analysis necessarily required modelling in addition to the estimation of the 6-month costs and QALYs from the trial. Consequently, a 6-month analysis was produced that represented observed (unmodelled) cost-effectiveness.

Costs and QALYs accruing after 6 months were modelled based on mortality rates, utilities and costs observed in the 4- to 6-month post-randomisation period. Use of rates and counts in the 4- to 6-month period was considered to represent the 'normal' pattern of care and natural history of the disease in this patient group. Therefore, using this is considered to be a reasonable estimate of future costs and outcomes.

Consequently, the mortality rate observed in the 4- to 6-month period was compared with that seen in the general population of England. The excess mortality seen in the trial population was then used to adjust pro rata subsequent age-specific annual mortality, and hence life expectancy, seen in the general population. The assumption here is that excess mortality is seen beyond 6 months, which is supported by the results of longer-term studies in the patient population.[48] The utility recorded at the 6-month follow-up was used to adjust age-specific general population utilities additively, and then combined with the life expectancy to produce an expected number of QALYs. The costs observed in the sixth month were combined with life expectancy to produce an expected cost. Both costs and QALYs were discounted at 3.5% per annum.

In this modelling no account is taken of the arm of the trial that the patients belong to; life expectancy, utility and cost relied only on age and gender. The mortality, utility decrement and cost figures from the trial used in the modelling of expected QALYs and costs were means from the entire trial. This is considered reasonable as, following the immediate treatment period, no long-lasting differences between treatments would be expected.

Data collection – recruited patients

The following data and variables were collected for all recruited patients (Appendix 9):

- physiological variables (pulse, non-invasive blood pressure, respiratory rate and oxygen

saturation) recorded on admission and at 1 and 2 hours after commencing the allocated intervention
- arterial blood gas analysis recorded on admission and 1 hour after commencing the allocated intervention
- patients were asked to score their severity of breathlessness on admission and at 1 and 2 hours after commencing the allocated intervention
- 12-lead electrocardiograms and biochemical markers of cardiac damage as clinically indicated
- clinical details such as patient demographics, preceding medical history and medication on admission
- in-hospital therapy including drug therapy, duration of interventional treatment, ventilatory pressures used (when appropriate)
- length of stay including duration of care in intensive or high dependency areas
- complications or adverse events, such as conjunctivitis, nasal skin trauma, gastric aspiration, pneumothorax
- treatment failure and intubation rate
- 7-day and in-hospital mortality.

Ethical and research governance

Ethics committee review

The trial was approved by the Multicentre Research Ethics Committee for Scotland (MREC/02/0/74), and individual local research ethics committees carried out a local review for each site. The trial complies with the current research governance policies and the MRC *Guidelines for Good Clinical Practice in Clinical Trials*.[49]

Research and development review

For each participating site, management approval was obtained from the local research and development department. Indemnity was provided via the relevant NHS indemnity scheme. Maintenance and repair of the ventilators was covered by an extended warranty agreement with the supplier for the duration of patient recruitment.

Trial registration

The trial is registered on Current Controlled Trials with registration number ISRCTN07448447 (www.controlled-trials.com).

Trial monitoring

Trial steering committee

This committee included a number of the grant applicants (AG, SG, ME) and, as requested by the Health Technology Appraisal (HTA) programme, three individuals (TC, RD, TMcD) not directly involved in the trial including a steering committee chair (TC). A member of a relevant consumer group (PH) also sat on this committee as well as an ex officio representative from the HTA programme (see Acknowledgements). This group met six times during the trial.

Trial management group

The trial management group met regularly and consisted of the grant applicants, the trial manager and the regional research nurses. This group met 12 times during the trial.

Local project groups

Each local site had a project group including the recruitment site clinical lead (emergency department consultant), a member of the senior nursing staff and middle grade medical staff for the emergency department and any other appropriate individuals. The regional research nurse and one of the grant applicants acted as a link between the local project groups and the trial management group.

Data monitoring committee

The data monitoring committee (DMC) analysed study data for monitoring purposes at 6-monthly intervals. This was a three-treatment comparison of standard oxygen therapy, CPAP and NIPPV. Two main questions were asked and rules that will lead to consideration of stopping were applied as follows.

Efficacy

The general principle was that stopping for reasons of efficacy would be triggered only by treatment group differences that were statistically significant at the 0.001 level. This avoids any serious distortion of the statistical significance of treatment differences due to multiple testing. It also avoids premature disclosure of unconvincing findings.

Using death, and then the combined end point of death or intubation, as the end point:

- If $p < 0.001$ (two-sided) terminate the worst of these treatments and then compare the best with standard therapy. If $p < 0.001$ terminate the trial. Otherwise continue to randomise to the best versus standard therapy.
- If $0.001 < p < 0.05$ do not terminate the worst (as we are not certain which this is) but compare only the best versus standard therapy (and if $p < 0.001$ terminate normal care).
- If $p > 0.05$ combine CPAP and NIPPV and then compare with standard therapy. If $p < 0.001$ terminate worst arm, i.e. terminate the trial if this is CPAP and NIPPV. Otherwise just terminate normal care.

Safety

The general principle was that if any of the principal outcomes was significantly worse at the 5% level of significance in either of the two active intervention arms, we would immediately consider termination of the inferior treatment. If the criteria below were met the DMC would consider the global position with all end points before recommending termination of any of the trial arms. As an illustration, if one treatment had a non-significantly improved mortality relative to standard care but a significantly worse intubation or MI rate, termination of this trial arm would not be automatic.

- If the mortality rate is significantly ($p < 0.05$) higher in patients randomised to either CPAP or NIPPV than in patients randomised to standard oxygen therapy, the inferior treatment will be dropped from future randomisations.
- If the intubation rate is significantly ($p < 0.05$) higher in patients randomised to either CPAP or NIPPV than in patients randomised to standard oxygen therapy, dropping the inferior treatment from future randomisation will be considered.
- If the MI rate is significantly ($p < 0.05$) higher in patients randomised to either CPAP or NIPPV than in patients randomised to standard oxygen therapy, dropping the inferior treatment from future randomisation will be considered.

At all times the DMC was guided by the above rules but not bound by them. All aspects of the trial and evidence from other studies were taken into account when making its recommendations.

Follow-up of non-recruited patients

Patients who were eligible for inclusion but not recruited were followed up to provide data to comply with CONSORT reporting for randomised controlled trials.[50] In addition, this information was required to monitor recruitment of eligible patients at each recruiting site. The Data Protection Act was complied with at all times. As a result of considerable variation in the availability of appropriate routine data, local site groups in conjunction with the regional trial research coordinator developed their own systems for the collection of data. Non-recruited patients were classified into groups to support delivery of site recruitment rates (*Table 2*).

Data management and security

All data collection forms sent from the clinical centres were input into project databases created in Microsoft ACCESS by the research team at the University of Sheffield. Data validation rules were written into the database where possible to minimise incorrect data entry. Data validation was carried out for each variable prior to analysis by analysing data ranges and examining outliers. Potential inaccuracies were checked against data collection forms and outstanding queries raised with the research contact at the clinical centres. Logical checks on related variables were also carried out (e.g. admission date after date of death). Input validation was carried out on a random sample of 5% of all eligible patients. We looked at 55 patients and 37 fields (taking each biochemical cardiac marker test, date, time, result as one field) and found three errors (one error each for three patients).

Data were collected, stored and used in accordance with the Data Protection Act 1998. All electronic data and trial documentation were stored in compliance with the ethics committee requirements. All information containing patient identifying details (recruitment form and consent forms) was stored in separate filing cabinets and separate databases. Any treatment and outcome data were referred to by study number only and had any patient-identifiable information removed. All documentation was kept in locked filing cabinets.

TABLE 2 *Non-recruited patient definitions*

1.	Missed (eligible but not considered for inclusion)
2.	Refused (patient refused initial consent)
3.	Too sick to consent (eligible but too sick to communicate consent and no relative is available to give assent)
4.	Communication problems (unable to consent because of language, deafness, aphasia)
5.	Clinician choice (eligible but deliberately excluded by the clinician)
6.	Previous participant in the study
7.	Randomisation service failure
8.	Non-invasive ventilation equipment not available
9.	Other (any patient who did not fit above)

All databases were stored on the computer hard drive of two members of the research team. Databases were password protected and the password was known only by three members of the research team. Databases were backed up on a data storage device each week.

Data will be archived and stored in secure storage at the University of Sheffield and the Royal Infirmary of Edinburgh for 7 years after the end of the trial (31 December 2007).

Changes to protocol

During the initial months of recruitment minor administrative changes were made to the trial protocol and paperwork to improve both readability and clarity. In June 2004 the Multicentre Research Ethics Committee for Scotland was consulted following discussions concerning how to handle data already collected on patients who subsequently refused continued participation at the point of retrospective consent (April 2004 trial management group, May 2004 trial steering committee meetings). The position adopted by the Committee was that:

> 'data collected following the initial consent and until the time the patient declines to continue can still be used for the purposes of the study analysis. The Committee considers that the initial consent was given in good faith and therefore the patient cannot retrospectively decline to participate. Clearly when the patient regains capacity and chooses not to continue then further data should not be collected.'

Following this clarification the retrospective information sheet and relative information sheet made it explicit that, if the participant refused retrospective consent, only data collected up to this time point would be used.

In September 2005 a review of the protocol resulted in rewording of the methods for the economic analysis but no significant change. Myocardial infarction was changed to a secondary end point, to be monitored throughout for patient safety. The recommended settings for using the ventilator were revised to maximise treatment effects and improve the scientific value of the results. The maximum level for CPAP was increased from 12.5 cmH_2O to 15 cmH_2O and guidance encouraged upping the titration in both modalities to the maximum tolerance over the first 15 minutes of treatment.

Recruitment extension

We initially anticipated that the required number of patients would be recruited in a 2-year period. This was subsequently extended to 47 months. The principal reasons are discussed below.

Trial set-up

1. *Bureaucracy of site set-up* This led to a prolonged set-up time at most sites (local research ethics committee/R&D approval/issues of indemnity/stakeholder resistance) of up to 1 year from initial contact.
2. *Staff training* Time taken to train sufficient emergency department staff to a safe level of proficiency to use the study equipment was longer than anticipated. For some sites there was no existing expertise (the use of the equipment and accompanying training was an incentive for some sites to participate). Set-up training provided by Respironics took longer than hoped because of their own

staffing shortages. Potential study patients were recruited as an emergency over a 24-hour period by attending clinical staff. This resulted in considerable time investment from the research team to ensure that all of these staff were trained to a proficient level. In addition, staffing shortages and pressures to meet 4-hour emergency department waiting time targets hampered training opportunities.

3. *Staggered site start-up* We were unable to start all sites at the same time because of the above and time required for input from research staff to set up each site.
4. *More trial sites than initially anticipated.* Increasing the number of recruiting sites from 17 to 26 took longer to administer. Negotiations took place with other sites that did not progress, and one site withdrew.

Study population

1. Fewer eligible patients presenting than projected from pilot studies.
2. Significant differences in eligible patients between sites.
3. Eligible patients too ill to provide informed consent.
4. Multiple presentations of patients with recurrent pulmonary oedema.

All of these issues were monitored throughout the project and measures taken to attempt to maximise recruitment.

Study sites

1. Variability in sustained commitment from individual sites impacted on projected recruitment targets for individual sites. Trial policy was to continue to support and promote a poorly recruiting site initially rather than withdrawing it. This was weighed against the time it takes to set up new sites and the additional expense involved in employing research staff in a geographically remote site. We issued each site with a realistic final target based on previous performance. One site withdrew from the trial.
2. Treatment preference and perception that the active treatment already works.
3. The 4-hour emergency department waiting target influenced the recruiting practice of the sites.

Chapter 3
Results

Of 1874 potentially eligible patients, 1511 were screened and 1156 randomised (*Figure 3*). A further 87 patients (*Table 3*) were excluded after randomisation because of ineligibility or previous recruitment into the trial, resulting in data being provided on 1069 for primary outcome analysis.

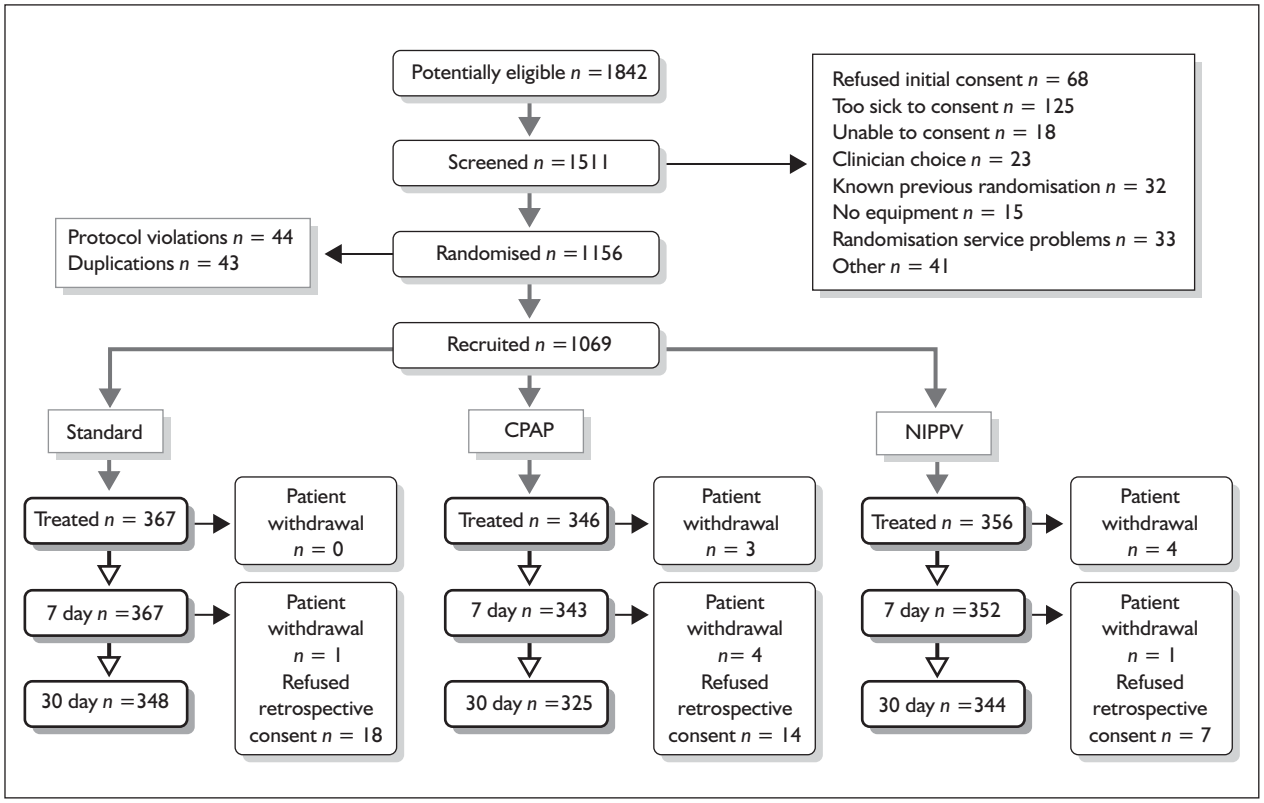

FIGURE 3 *Flow diagram for the 3CPO trial.*

TABLE 3 *Reasons for exclusion after enrolment*

	Standard therapy	CPAP	NIPPV	Total
Did not meet inclusion criteria	1	6	5	12
Previous inclusion in 3CPO study	14	18	11	43
Inability to provide informed consent at any time within the trial period	2	3	3	8
Inadequate consent gained before randomisation	3	4	4	11
Patient details recorded by randomisation system but no evidence found in hospital records	2	0	2	4
Data collection and consent forms lost	0	2	3	5
No details available	1	3	0	4
Total	23	36	28	87

Description of patients and comparability between groups

Patients were elderly (mean age ± SD: 77.8 ± 9.7 years), predominantly female (57%) and unwell with a marked tachycardia (mean pulse rate/min ± SD: 113 ± 22), tachypnoea (mean respiratory rate/min ± SD: 32 ± 7), hypertension (mean systolic blood pressure ± SD: 162 ± 36 mmHg), acidosis (mean SD: pH7.22 ± 0.09) and hypercapnia (mean ± SD: 7.6 2.2 kPa) (*Tables 4* and *5*). They had significant co-morbidities [ischaemic heart disease (63%), congestive cardiac failure (44%), chronic obstructive pulmonary disease (18%) and hypertension (56%)]; 22% had symptoms of myocardial ischaemia at presentation.

TABLE 4 *Patient characteristics: medical history and routine medication*

	Standard therapy	CPAP	NIPPV	All	*p*-value[a]
Number	367	346	356	1069	
Age (years), mean ± SD	78.5 ± 9.1	77.6 ± 10.2	77.2 ± 9.9	77.8 ± 9.7	0.227
Sex (male)	42%	45%	43%	43%	0.788
Past medical history (%)					
Ischemic heart disease (*n* = 1048)	64	64	60	63	0.451
Congestive heart failure (*n* = 1046)	45	42	47	44	0.403
Valvular heart disease (*n* = 1043)	12	11	9	11	0.677
COPD (*n* = 1049)	19	15	21	18	0.178
Hypertension (*n* = 1038)	56	55	57	56	0.878
Diabetes mellitus (*n* = 1053)	30	30	33	31	0.573
Hypercholesterolaemia (*n* = 1027)	30	33	31	32	0.712
Current smoker (*n* = 1036)	16	19	19	18	0.584
PVD (*n* = 1040)	10	11	10	10	0.891
Cerebrovascular disease (*n* = 1050)	18	17	16	17	0.879
Regular medications (%)					
Antiplatelet therapy (*n* = 1041)	62	65	63	63	0.821
Anticoagulant therapy (*n* = 1042)	14	11	13	13	0.453
ACE inhibitor/ARB (*n* = 1033)	38	41	43	41	0.473
Aldosterone antagonist (*n* = 1029)	3	4	6	4	0.245
Diuretic (*n* = 1035)	63	61	64	63	0.552
Beta-blocker (*n* = 1032)	31	36	38	35	0.110
Calcium antagonist (*n* = 1024)	19	18	23	20	0.312
Nitrate (*n* = 1031)	22	26	26	24	0.388
Nicorandil (*n* = 1041)	7	9	8	8	0.662
Theophyllines (*n* = 1040)	2	1	1	1	0.663
Oral steroids (*n* = 1041)	7	5	5	6	0.532
Inhaled steroids (*n* = 1044)	16	11	10	12	0.046
Bronchodilator inhalers (*n* = 1041)	19	13	17	16	0.120

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease.
a All *p*-values are for a chi-squared test, except for age which uses one-way analysis of variance.

TABLE 5 *Patient characteristics: physiology, arterial blood gas exchange and symptoms*

	Standard therapy	CPAP	NIPPV	All	*p*-value[a]
Baseline physiology					
Pulse rate (per minute) (*n* = 1060)	114 ± 24	113 ± 21	112 ± 22	113 ± 22	0.380
Systolic blood pressure (mmHg) (*n* = 1057)	161 ± 38	162 ± 35	161 ± 36	162 ± 36	0.947
Diastolic blood pressure (mmHg) (*n* = 1054)	87 ± 25	89 ± 23	87 ± 24	88 ± 24	0.471
Respiratory rate (per minute) (*n* = 1053)	33 ± 7	32 ± 7	32 ± 7	32 ± 7	0.203
Oxygen saturation (%) (*n* = 1052)	92 (86–97)	92 (86–97)	92 (85–97)	92 (86–97)	0.936
Arterial pH (*n* = 1053)	7.22 ± 0.08	7.21 ± 0.09	7.22 ± 0.09	7.22 ± 0.09	0.321
Arterial pO_2 (kPa) (*n* = 1049)	10.7 (8.3–14.9)	10.9 (8.5–16.5)	10.3 (8.4–15.5)	10.6 (8.4–15.6)	0.617
Arterial pCO_2 (kPa) (*n* = 1052)	7.6 ± 2.5	7.5 ± 1.9	7.7 ± 2.3	7.6 ± 2.2	0.525
Bicarbonate (mmol/l) (*n* = 1003)	21 ± 4	21 ± 4	21 ± 5	21 ± 4	0.725
Patient symptoms					
Symptom of MI at presentation (*n* = 1039)	22%	22%	22%	22%	0.980
Patient self-reported dyspnoea (*n* = 657)	10 (8–10)	10 (8–10)	10 (8–10)	10 (8–10)	0.551

All values are mean ± standard deviation and *p*-values are for one-way analysis of variance, except for oxygen saturation, arterial pO_2 and dyspnoea, which report median values (interquartile range) and use a Kruksal–Wallis test for significance, and symptoms of MI at presentation, which uses a chi-squared test.

Trial intervention

Patients and concomitant therapies were evenly allocated across the intervention arms (*Figure 3* and *Table 6*). Although overall completion rates were similar, standard oxygen therapy was associated with a greater failure rate due to respiratory distress, whereas non-invasive ventilation was less well tolerated, especially NIPPV (*Table 7*). The mean (SD) duration of CPAP therapy was 2.2 ± 1.5 hours and of NIPPV therapy was 2.0 ± 1.3 hours.

Trial patients received significant concomitant therapies [loop diuretics (89%), nitrates (90%) and opioids (51%)].

Primary outcomes

There was no difference in the primary end point of 7-day mortality between non-invasive ventilation (CPAP or NIPPV) (9.5% mortality) and standard oxygen therapy (9.8% mortality) [odds ratio (OR) 0.97, 95% CI 0.63–1.48; $p = 0.87$] (*Figure 4* and *Table 8*). The 7-day mortality in non-recruited patients was 9.9% (see section on non-recruited patients).

The primary composite end point of 7-day mortality and intubation rate (*Figure 4* and *Table 9*) was similar for CPAP and NIPPV (11.7% versus 11.1% respectively; OR 0.94, 95% CI 0.59–1.51; $p = 0.81$).

Secondary outcomes

There was no difference in 30-day mortality between standard oxygen therapy and non-invasive ventilation (16.4% and 15.2% respectively) (OR 0.92, 95% CI 0.64–1.31; $p = 0.64$; *Table 8*). The 7- and 30-day mortality rates were similar for CPAP

TABLE 6 *Trial allocation and treatment*

	Standard therapy	CPAP	NIPPV	All	*p*-value[a]
Initial treatment[b]					
Nitrate therapy ($n = 1054$)	93%	88%	91%	90%	0.11
Diuretic therapy ($n = 1057$)	90%	89%	89%	89%	0.89
Opioid therapy ($n = 1054$)	55%	50%	49%	51%	0.31
Inspired oxygen (l/min) ($n = 983$)	12 ± 4	12 ± 4	12 ± 4	12 ± 4	0.44
Ventilation pressure (cmH_2O)	–	10 ± 4	14 ± 5/7 ± 3	–	
Treatment allocation					
Treatment allocated	367	346	356	1069	
Started allocated treatment[c]	365/366 (99.7%)	337/343 (98.3%)	344/354 (97.2%)	1046/1063 (98.4%)	0.02

a *p*-value is for chi-squared test.
b All ± figures are SD.
c Details for six patients were missing.

TABLE 7 *Patients failing to complete allocated treatment: 'crossovers'*

Standard therapy		CPAP	NIPPV	All	*p*-value[a]
Completed allocated treatment[b]	298/363 (82.1%)	285/340 (83.8%)	267/352 (75.9%)	850/1055 (80.6%)	0.02
Treatment changed to:	Intubation: 3; CPAP: 43; NIPPV: 13; not stated: 6	Intubation: 1; standard: 31; NIPPV: 5; not stated: 18	Intubation: 4; standard: 49; CPAP: 12; not stated: 20		
Reason for not completing treatment allocation					
Not tolerated	1 (0.3%)	18 (5.2%)	30 (8.4%)		< 0.001
Worsening arterial blood gas parameters	26 (7.1%)	10 (2.9%)	15 (4.2%)		0.03
Respiratory distress	31 (8.4%)	5 (1.4%)	12 (3.4%)		< 0.001
Other reason	18 (4.9%)	24 (6.9%)	29 (8.1%)		0.21

a *p*-value is for chi-squared test.
b Details for 14 patients were missing.

and NIPPV (9.6% versus 9.4% and 15.4% versus 15.1%; OR 0.97 and 0.98; $p = 0.91$ and $p = 0.92$ respectively; *Table 9*).

Non-invasive ventilation (CPAP and NIPPV) resulted in greater reductions in breathlessness, heart rate, acidosis and hypercapnia than standard oxygen therapy (*Table 8*). Rates of tracheal intubation, critical care admission (intensive or coronary care) and MI were similar for non-invasive ventilation compared with standard oxygen therapy, and for CPAP compared with NIPPV (*Table 9*).

Figure 5 describes in detail the physiological variables across all groups at 0, 1 and 2 hours after recruitment.

Subgroup analysis

There was no interaction between treatment effect upon 7-day mortality and illness severity (the prespecified subgroup analysis), whether defined a priori by baseline arterial pH ($p = 0.94$) or post hoc by systolic blood pressure ($p = 0.17$). Further post hoc exploratory subgroup analysis found no

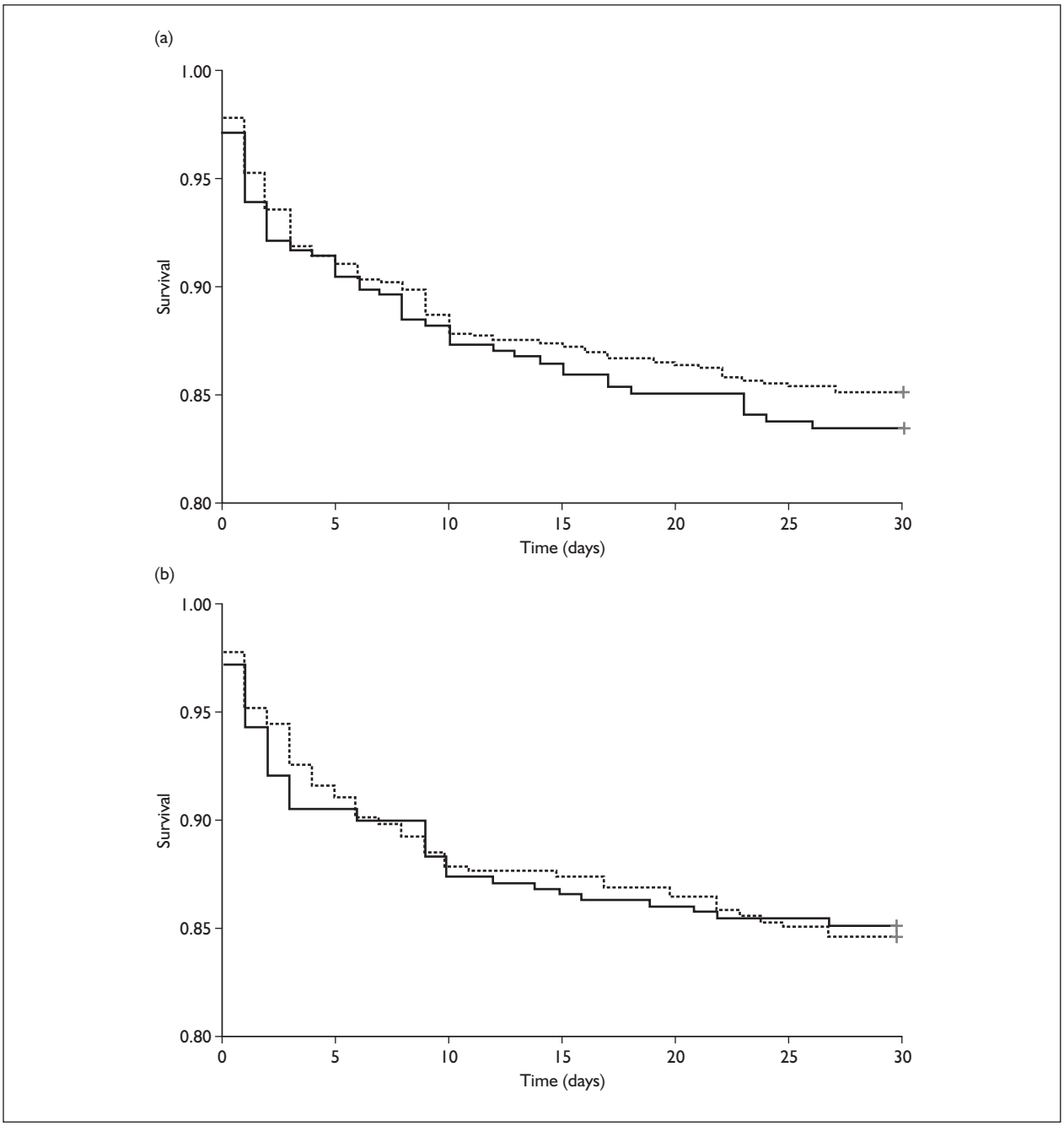

FIGURE 4 *(a) Kaplan–Meier survival curve for comparison between standard oxygen therapy (solid line) and non-invasive ventilation (CPAP or NIPPV; dotted line). (b) Kaplan–Meier survival curve for comparison between CPAP and NIPPV.*

interactions between treatment effect and age ($p = 0.52$), gender ($p = 0.33$), previous history of heart failure ($p = 0.28$) and MI at presentation ($p = 0.93$).

Treatment crossovers (*Table 7*) had higher 7-day mortality than those who completed their allocated treatment (19.8% versus 7.1%; $p < 0.001$). If all crossovers are excluded, the 7-day mortality rates are 7.6% for non-invasive ventilation versus 6.0% for standard therapy (OR 1.29, 95% CI 0.73–2.28; $p = 0.388$), and 7.4% for CPAP versus 7.9% for NIPPV (OR 0.93, 95% CI 0.50–1.75; $p = 0.825$). However, when treatment groups were analysed separately only the standard therapy group showed a significant difference in baseline pH between those patients who did and those who did not complete the treatment arm (7.230 versus 7.186; $p < 0.001$). No group showed any significant difference in baseline systolic blood pressure between those patients who did and those who did not complete the treatment arm. In conclusion, there is some evidence that the standard therapy crossovers were more severely ill.

TABLE 8 *Primary and secondary end points [standard oxygen therapy vs non-invasive ventilation (CPAP or NIPPV)]*

	Standard therapy	NIPPV + CPAP	Odds ratio	95% CI	*p*-value[a]
Primary end point					
7-day mortality	9.8%	9.5%	0.97	0.63–1.48	0.87
Secondary end points					
30-day mortality	16.4%	15.2%	0.92	0.64–1.31	0.64
Intubation	2.8%	2.9%	1.05	0.49–2.27	0.90
Critical care admission	40.5%	45.2%	1.21	0.93–1.57	0.15
Myocardial infarction					
WHO criteria	24.9%	27.0%	1.12	0.84–1.49	0.46
ESC/ACC criteria	50.5%	51.9%	1.06	0.82–1.36	0.66
			Difference between means	**95% CI**	***p*-value[a]**
Length of hospital stay (days)	10.5	11.4	0.9	–0.2 to 2.0	0.10
Patient dyspnoea (delta 0–1 hour)	3.9	4.6	0.7	0.2–1.3	0.008
Physiology (delta 0–1 hour)					
Pulse rate (per minute)	13	16	4	1–6	0.004
Systolic blood pressure (mmHg)	34	38	3	–1 to 8	0.17
Diastolic blood pressure (mmHg)	22	22	0	–3 to 3	0.95
Respiratory rate (per minute)	7.1	7.2	0.2	–0.8 to 1.1	0.74
Oxygen saturation (%)	3.5	3	–0.4	–1.4 to 0.6	0.41
Arterial pH	0.08	0.11	0.03	0.02–0.04	< 0.001
Arterial pO_2 (kPa)	0.7	–0.6	–1.2	–2.6 to 0.1	0.07
Arterial pCO_2 (kPa)	0.8	1.5	0.7	0.4–0.9	< 0.001
Bicarbonate (mmol/l)	1.7	1.8	0.1	–0.7 to 1.0	0.77

a *p*-values are for unadjusted logistic regression for binary variables and *t*-test for continuous variables.

Complications, side effects and adverse events

Tables 10 and *11* describe complications occurring within 24 hours of recruitment not directly related to the trial intervention and side effects that could be directly attributable to non-invasive ventilation respectively. There were no recorded serious adverse events during trial recruitment. There was no statistical or clinically significant difference between any intervention- or non-intervention-related side effect or complication.

Patient satisfaction

A total of 472 patients completed at least part of the patient satisfaction questionnaire. A further 276 patients returned the questionnaire saying that they had no memory of their time in the emergency department and therefore felt unable to complete the questionnaire. There was no difference in age or gender of respondents between the treatment groups. Respondents were slightly younger than non-respondents (mean 77.0 versus 78.4 years; $p = 0.028$) and included a larger proportion of men (47% versus 40%; $p = 0.018$) (*Table 12*).

The proportion of patients rating each element as 'excellent' ranged from 23% for advice about ways to avoid illness and stay healthy (which also had a high proportion of missing data), to 58% for overall satisfaction with the service received. There was no significant difference in satisfaction between

TABLE 9 *Primary and secondary end points (CPAP vs NIPPV)*

	CPAP	NIPPV	Odds ratio	95% CI	*p*-value[a]
Primary end point					
7-day mortality or intubation	11.7%	11.1%	0.94	0.59–1.51	0.81
Secondary end points					
7-day mortality	9.6%	9.4%	0.97	0.58–1.61	0.91
30-day mortality	15.4%	15.1%	0.98	0.64–1.49	0.92
Intubation	2.4%	3.5%	1.48	0.60–3.67	0.40
Critical care admission	44.5%	45.8%	1.06	0.78–1.43	0.73
Myocardial infarction					
WHO criteria	27.2%	26.8%	0.98	0.70–1.37	0.90
ESC/ACC criteria	49.1%	54.7%	1.25	0.93–1.69	0.14
			Difference between means	**95% CI**	***p*-value**
Length of hospital stay (days)	11.3	11.5	0.2	–1.1 to 1.5	0.81
Patient dyspnoea (delta 0–1 hour)	4.7	4.5	–0.2	–0.8 to 0.4	0.52
Physiology (delta 0–1 hour)					
Pulse rate (per minute)	17	15	–2	–5 to 1	0.26
Systolic blood pressure (mmHg)	38	37	–1	–6 to 5	0.77
Diastolic blood pressure (mmHg)	23	21	–2	–6 to 2	0.31
Respiratory rate (per minute)	7.3	7.1	–0.1	–1.2 to 1	0.82
Oxygen saturation (%)	3.5	2.6	–0.9	–2..2 to 0.3	0.14
Arterial pH	0.12	0.1	–0.01	–0.02 to 0	0.05
Arterial pO_2 (kPa)	–1.1	0	1.2	–0.5 to 2.8	0.16
Arterial pCO_2 (kPa)	1.5	1.4	–0.1	–0.3 to 0.2	0.67
Bicarbonate (mmol/l)	2.3	1.3	–0.9	–1.8 to 0	0.04

a *p*-values are for unadjusted logistic regression for binary variables and for *t*-test for continuous variables.

treatment groups for any of the patient satisfaction measures (*Table 13*).

Long-term follow up, use of resource and quality of life

One year after the last patient was recruited, the details of all patients who had provided consent were sent to the NHS Information Centres for England and Scotland to identify all deaths. Of the original cohort, 39 declined to give repeat consent and six patients withdrew from the trial leaving 1024 patients eligible for longer-term follow-up. Survival curves for each arm are shown in the Kaplan–Meier plot (*Figure 6*); there was no difference between the three treatment groups ($p = 0.964$, log-rank test).

Data were collected on the use of other cardiovascular interventions (investigations and treatment) up to the time of discharge from hospital. *Table 14* details the more common interventions. As can be seen there is no difference in any of the parameters between the three trial intervention groups.

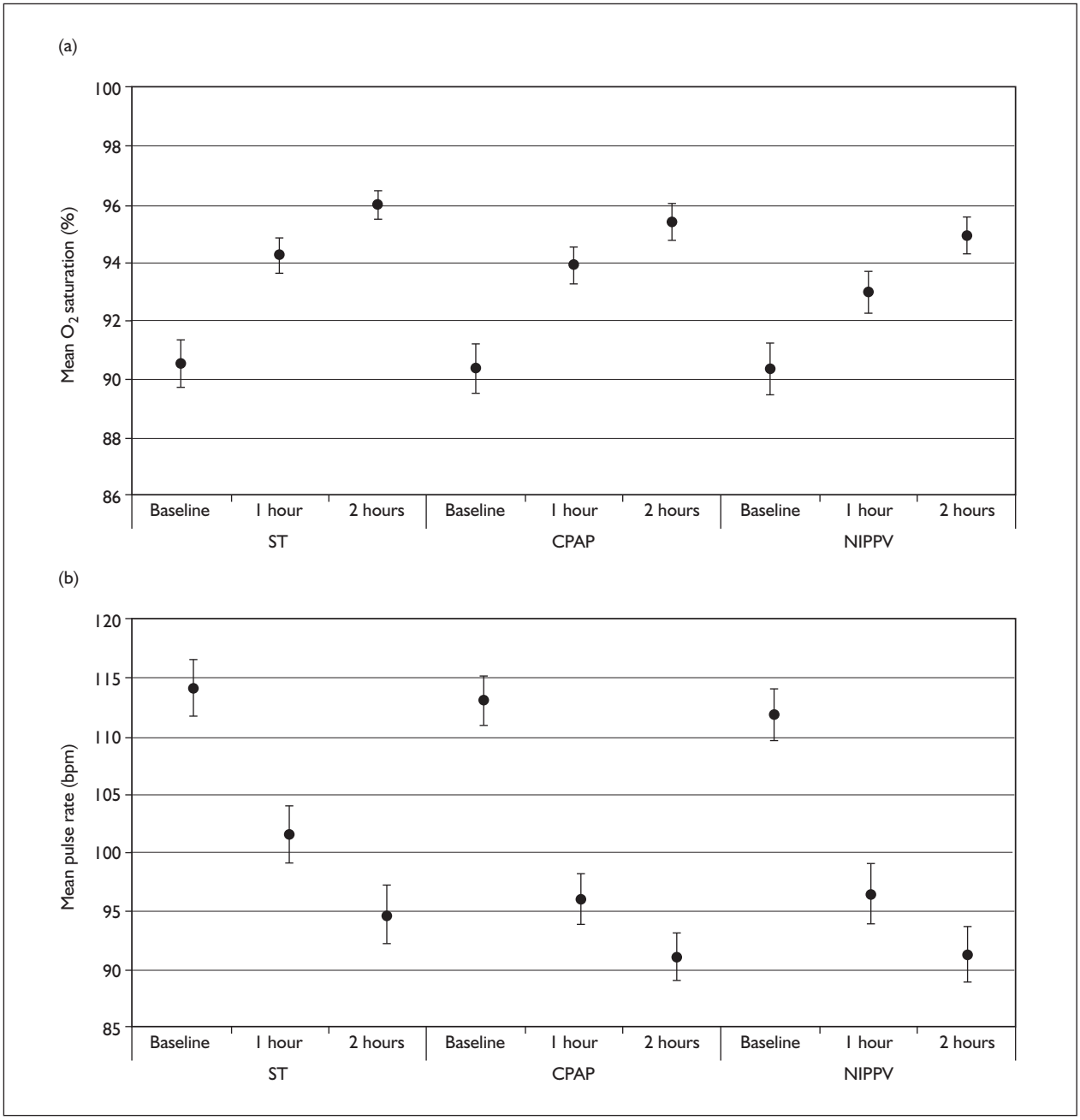

FIGURE 5 *Physiological variables at 0, 1 and 2 hours: (a) oxygen saturations, (b) pulse rate, (c) respiratory rate, (d) systolic blood pressure, (e) diastolic blood pressure and (f) mean blood pressure. Error bars represent the standard error.*

Recruitment and sites

In total, 26 emergency departments recruited patients for the trial. Geographical areas and sites are described in *Figure 7* and *Table 15*. The total number of patients recruited by site is detailed in *Figure 8*. Cumulative patients recruited during the trial and monthly recruitment numbers are detailed in *Figures 9* and *10* respectively.

Follow-up of non-recruited patients

Data were collected on all potentially eligible patients who were not recruited to comply with CONSORT reporting and to ensure adequate recruitment of eligible patients at each site. Reasons for non-recruitment are described in Chapter 2. Overall, 60% of potentially eligible patients and 73% of truly eligible patients (i.e. met all inclusion and no exclusion criteria) were

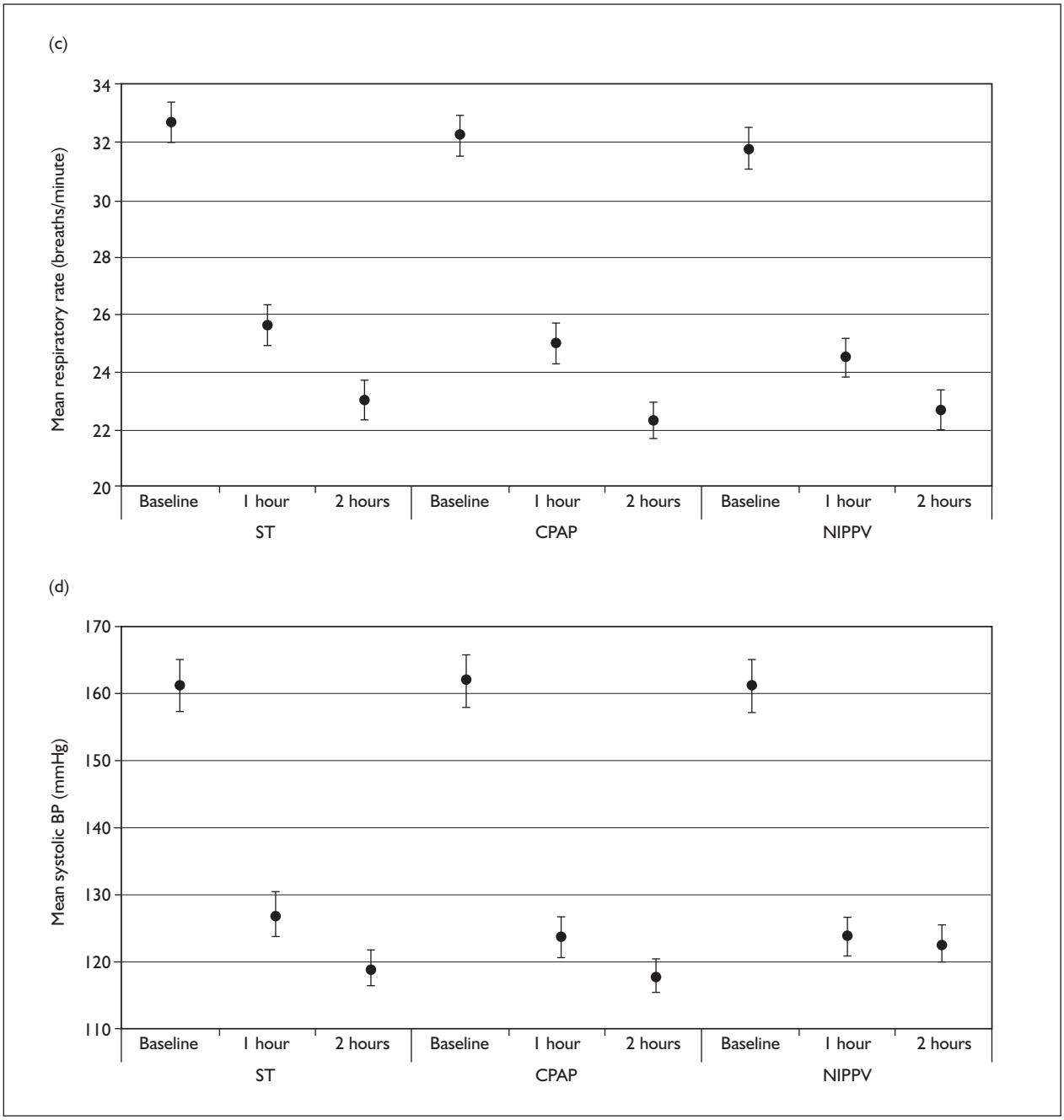

FIGURE 5 *(continued) Physiological variables at 0, 1 and 2 hours: (a) oxygen saturations, (b) pulse rate, (c) respiratory rate, (d) systolic blood pressure, (e) diastolic blood pressure and (f) mean blood pressure. Error bars represent the standard error.*

recruited during the study period. *Table 16* and *Figures 11* and *12* detail the reasons for non-recruitment across all sites during the trial period, the proportion of truly eligible patients recruited at each site and the proportion of truly eligible patients recruited for each 3-month period respectively. The recruitment rate was significantly higher than the 50% of truly eligible patients anticipated in the original proposal.

The 7-day mortality rate for non-recruited patients was 9.2% and median length of hospital stay was 8 days (all non-significant in comparison with recruited patients).

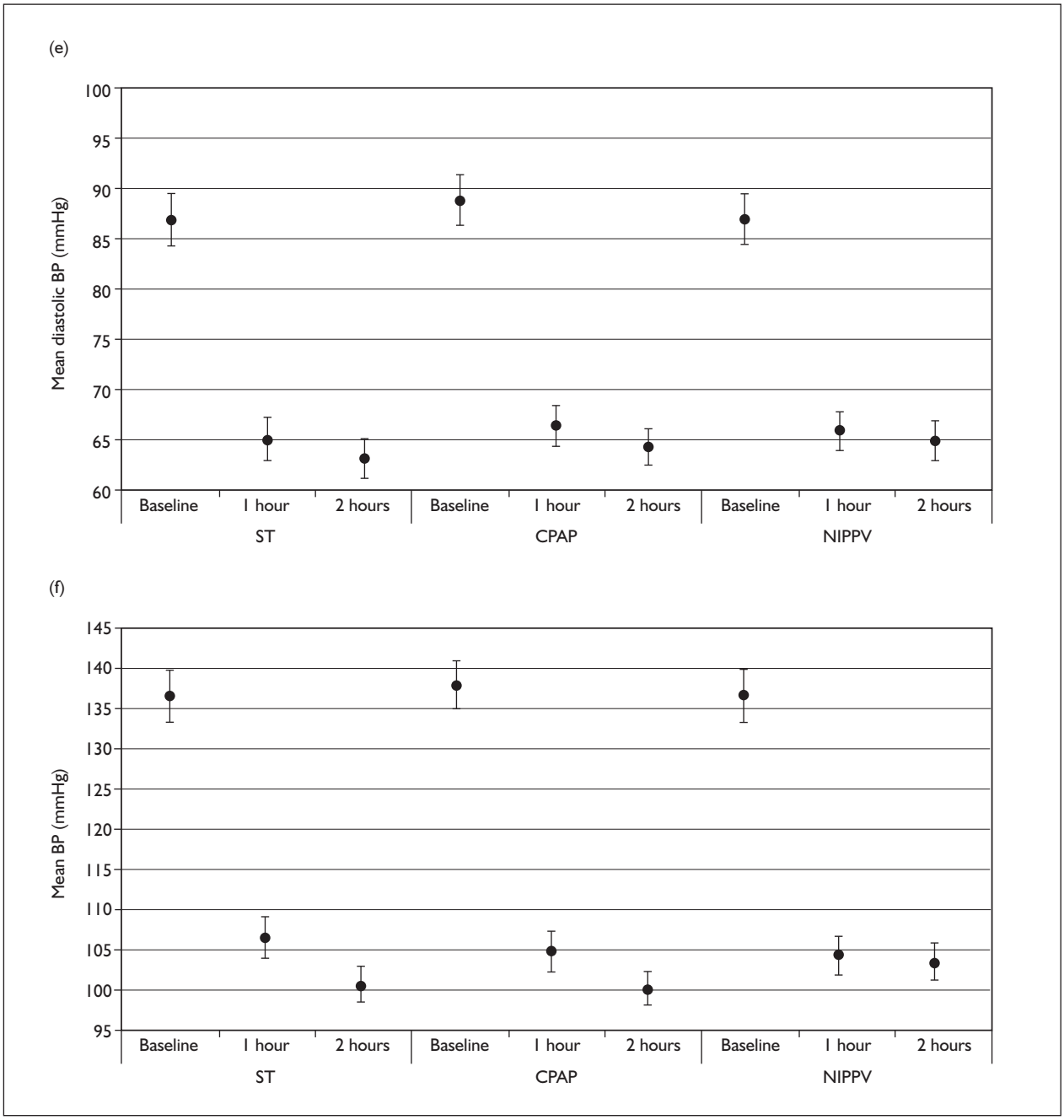

FIGURE 5 *Physiological variables at 0, 1 and 2 hours: (a) oxygen saturations, (b) pulse rate, (c) respiratory rate, (d) systolic blood pressure, (e) diastolic blood pressure and (f) mean blood pressure. Error bars represent the standard error.*

TABLE 10 *Complications within 24 hours not specifically related to CPAP or NIPPV*

	Standard therapy	CPAP	NIPPV	*p*-value[a]
Vomiting	6/357	6/334	8/347	0.816
Gastric aspiration	0/357	0/333	1/347	0.371
Hypotension	46/352	36/332	37/346	0.548
Arrhythmia requiring treatment	23/350	12/332	25/345	0.102
Pneumothorax	0/356	0/333	1/346	0.369
Progressive respiratory distress	35/354	17/333	21/346	0.034
Cardiorespiratory arrest	16/355	6/333	10/345	0.119
Any other complication	23/353	18/329	18/345	0.737

a *p*-value for chi-squared test.

TABLE 11 *Side effects due to active intervention*

	CPAP	NIPPV	*p*-value[a]
Facial skin necrosis	0/287	0/291	–
Face discomfort	14/281	15/292	0.909
Increased breathing discomfort	11/285	16/291	0.352
Other side effect	16/287	19/291	0.631

a *p*-value for chi-squared test.

TABLE 12 *Characteristics of respondents*

	Standard therapy	CPAP	NIPPV	All	*p*-value[a]
Mean age (years)	77.8	76.9	76.4	77.0	0.440
Male	47% (72/155)	53% (76/144)	43% (74/173)	47% (222/472)	0.203

a *p*-value is chi-squared test for age, one-way analysis of variance for age.

TABLE 13 *Patient satisfaction – percentage of patients rating each element as 'excellent'.*

	Standard therapy	CPAP	NIPPV	All	*p*-value[a]
The thoroughness of examinations and accuracy of diagnosis	49 (74/152)	46 (65/140)	52 (87/169)	49 (226/461)	0.673
The skill, experience and training of hospital staff	45 (67/150)	46 (64/140)	52 (86/167)	47 (217/457)	0.421
The thoroughness of treatment	50 (76/151)	44 (61/139)	54 (91/169)	50 (228/459)	0.216
Explanations given to you about medical procedures and tests	38 (55/144)	36 (48/135)	42 (68/162)	39 (171/441)	0.520
Attention given to what you have to say	40 (58/146)	35 (44/127)	42 (68/163)	39 (170/436)	0.461
Advice you got about ways to avoid illness and stay healthy	20 (16/81)	17 (12/69)	30 (24/81)	23 (52/231)	0.154
Friendliness and courtesy shown to you by hospital staff	56 (84/149)	50 (70/139)	61 (102/166)	56 (256/454)	0.151
Personal interest in you and your medical problems	44 (64/146)	38 (51/133)	50 (82/166)	44 (197/445)	0.159
Respect shown to you, and attention to your privacy	46 (68/148)	46 (63/137)	54 (89/166)	49 (220/451)	0.293
Reassurance and support offered to you by hospital staff	49 (72/147)	42 (56/135)	47 (78/165)	46 (206/447)	0.419
Amount of time the hospital staff gave you	43 (63/147)	41 (54/133)	49 (81/165)	45 (198/445)	0.303
Overall, how satisfied are you with the service you received?	60 (91/151)	52 (69/134)	62 (103/167)	58 (263/452)	0.168

a *p*-value for chi-squared test.

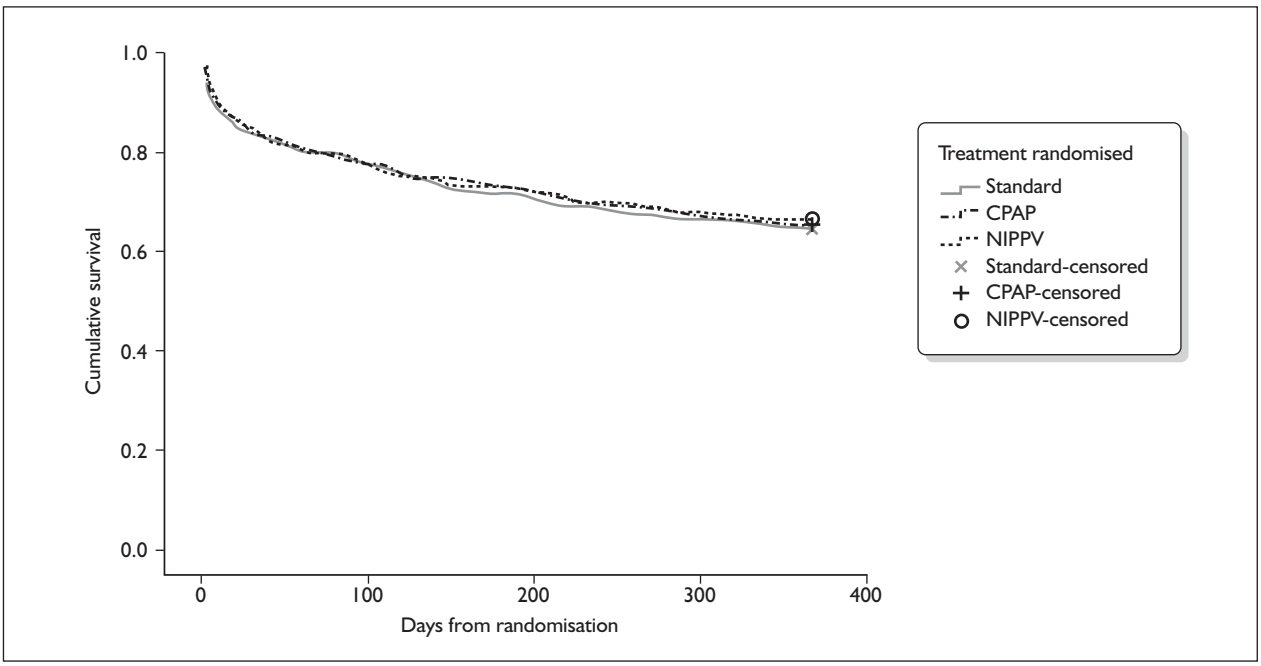

FIGURE 6 *Survival to 12 months from recruitment (all three arms).*

TABLE 14 *Use of other common cardiovascular interventions*

	ST	CPAP	NIPPV	*p*-value[a]
Intravenous thrombolysis	5/335	4/310	3/328	0.792
PTCA or coronary stenting	16/335	22/310	20/330	0.458
CABG	4/335	8/309	2/329	0.099
Other cardiac surgery	9/335	5/309	10/329	0.487
Cardiac inotropes	11/337	9/310	9/328	0.921
Intra-aortic balloon pump	5/336	2/309	1/327	0.222
Echocardiogram	160/336	147/308	178/330	0.180
Thallium scanning	0/336	0/306	0/326	–

CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty.
a *p*-value for chi-squared test.

FIGURE 7 *Recruiting sites.*

TABLE 15 *Recruiting sites in Scotland and England (listed in order of start date)*

Hospital	Location	Start	Finish
Northern General Hospital	Sheffield	19/07/03	30/04/07
Royal Infirmary of Edinburgh	Edinburgh	21/07/03	30/04/07
Frenchay Hospital	Bristol	04/09/03	30/04/07
Ninewells Hospital	Dundee	15/09/03	14/02/06
Royal United Hospital	Bath	15/09/03	30/04/07
York Hospital	York	24/09/03	30/04/07
Southern General Hospital	Glasgow	01/10/03	30/04/07
Birmingham Heartlands Hospital	Birmingham	03/11/03	24/05/06
St James's University Hospital	Leeds	12/11/03	30/04/07
Leeds General Infirmary	Leeds	19/11/03	30/04/07
Harrogate Hospital	Harrogate	12/01/04	30/04/07
Selly Oak Hospital	Birmingham	12/01/04	22/09/06
Barnsley Hospital	Barnsley	16/01/04	30/04/07
Crosshouse Hospital	Kilmarnock	05/07/04	30/04/07
Hope Hospital	Salford, Manchester	05/07/04	30/04/07
Hairmyres Hospital	East Kilbride	28/10/04	30/04/07
Whiston Hospital	Prescot, Merseyside	09/11/04	30/04/07
The Princess Royal University Hospital	Farnborough	29/11/04	14/02/06
Royal Devon and Exeter Hospital	Exeter	31/01/05	30/04/07
Manchester Royal Infirmary	Manchester	31/01/05	30/04/07
Bristol Royal Infirmary	Bristol	01/02/05	30/04/07
Torbay Hospital	Torquay	16/02/05	30/04/07
Wythenshawe Hospital	Manchester	04/04/05	30/04/07
Warrington Hospital	Warrington	31/05/05	30/04/07
The James Cook University Hospital	Middlesbrough	04/10/05	30/04/07
Pinderfields Hospital	Wakefield	25/08/06	30/04/07

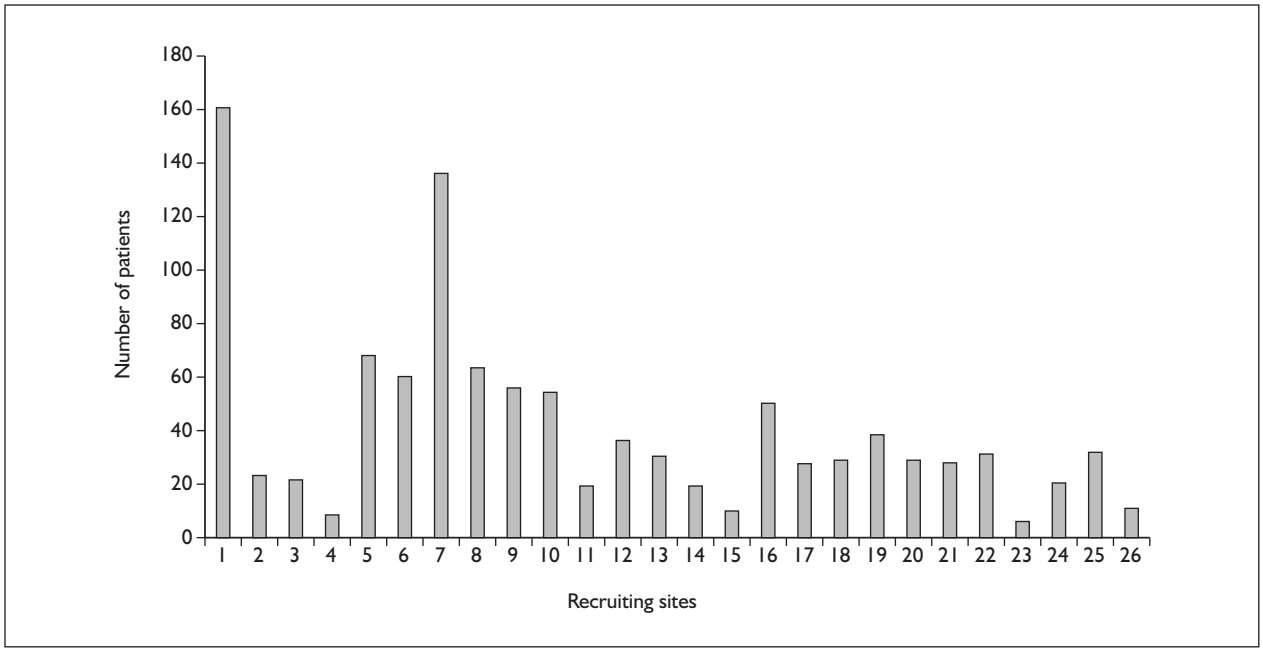

FIGURE 8 *Number of patients recruited per site.*

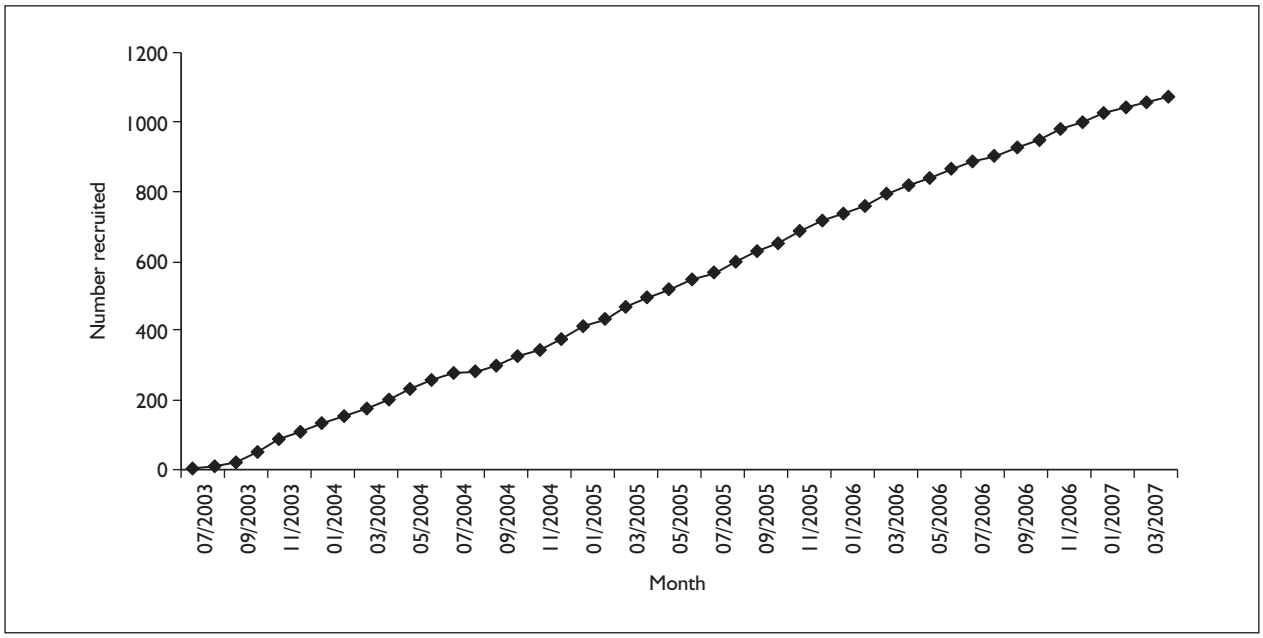

FIGURE 9 *Cumulative number of patients recruited during trial.*

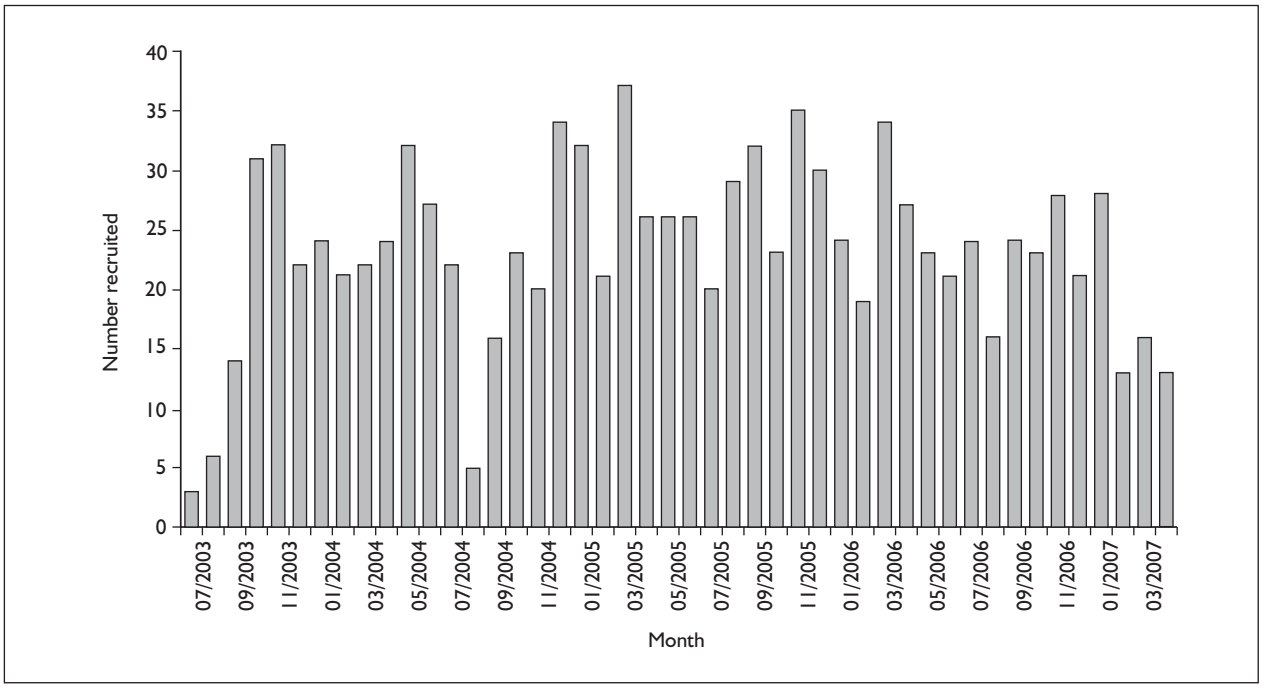

FIGURE 10 *Monthly recruitment.*

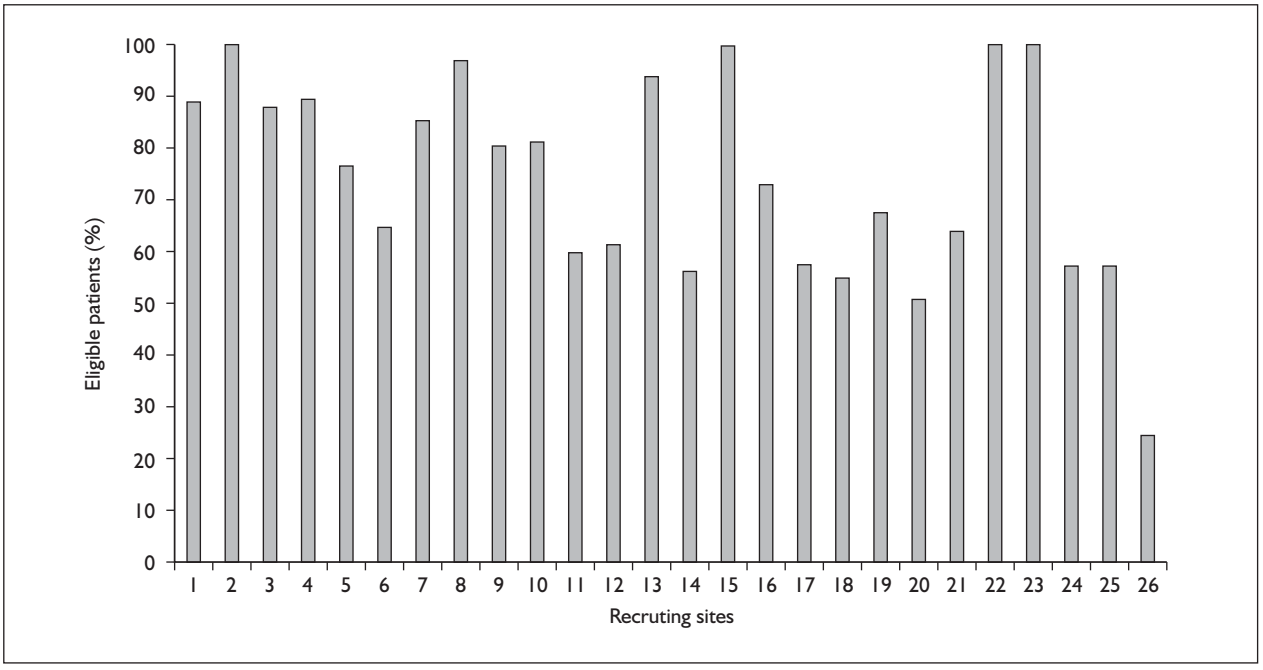

FIGURE 11 *Recruitment rates for each recruiting site.*

TABLE 16 *Reasons for non-recruitment*

Reason	*n*	Mean (SD) age, years	Male, *n* (%)	7-day mortality, *n* (%)	Admitted to ICU, *n* (%)	Median (IQR) length of stay, days
Patients not randomised to trial						
Missed	363	78 (10)	150 (42)	29 (9)	15 (4)	8 (5–13)
Refused consent	68	78 (10)	17 (25)	3 (5)	0	7 (4–12)
Too sick for initial consent	125	79 (12)	54 (43)	19 (17)	7 (6)	8 (4–13)
Unable to consent because of language, cognition, etc.	18	77 (13)	13 (72)	2 (11)	2 (11)	11 (3–18)
Clinician choice	23	74 (11)	11 (48)	2 (10)	0	9 (3–15)
Randomisation service problems	33	77 (11)	17 (52)	3 (11)	1 (4)	7 (3–14)
Equipment not available	15	79 (12)	6 (43)	2 (15)	0	9 (5–15)
Other	32	80 (10)	16 (50)	2 (8)	2 (8)	7 (5–12)
Not recorded	9	–	–	–	–	–
All non-randomised	686	78 (11)	288 (42)	63 (9.2)	28 (5)	8 (4–13)
Patients randomised and excluded before intervention						
Refused consent	7	–	–	–	–	–
Too sick for initial consent	1	–	–	–	–	–
Unable to consent due to language, cognition etc	1	–	–	–	–	–
Duplicate	43	79 (8)	–	–	–	–
Equipment not available	1	–	–	–	–	–
Other	5	–	–	–	–	–
Not recorded	11	–	–	–	–	–
Found not to meet inclusion criteria	18	82 (12)	–	–	–	–
All randomised and excluded	87	80 (10)	–	–	–	–

IQR, interquartile range.

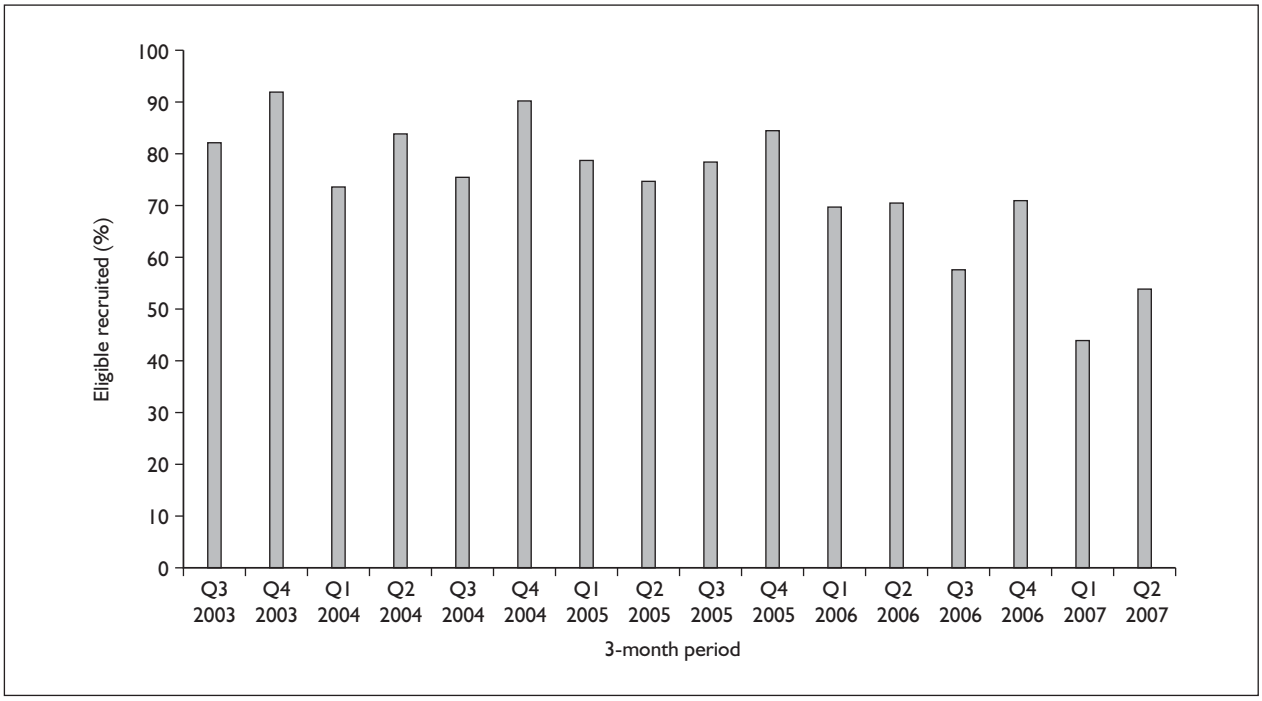

FIGURE 12 *Proportion of eligible patients recruited per 3-month period during the trial.*

Chapter 4
Health economics

Unit costs and microcosting

Table 17 shows the unit costs used for the economic evaluation. The unit costs for the initial emergency department episode in each study group, which are derived from the microcosting study, are included in *Table 17* and its constituent unit costs are shown in *Table 18*. The estimated cost per patient of the Respironics Synchrony machine used to provide non-invasive ventilation was £86, based on the costs outlined in *Tables 19* and *20*. A detailed breakdown of the emergency episode unit cost is shown in *Table 21*. As expected, the microcosting estimates for CPAP and NIPPV are markedly higher than that for standard therapy, reflecting the additional costs of the machine and additional staff time required to operate it.

Six-month data

Questionnaires were sent to 668 participants at 1 month, 625 at 3 months and 573 at 6 months. The response rates were 77.2%, 73.9% and

TABLE 17 *Unit costs used in the economic evaluation*

Trial costs	Cost (£) (2006/7)	Source
Standard emergency department care for ACPO	298	Microcosting study (*Tables 18–21*)
CPAP	430	Microcosting study (*Tables 18–21*)
NIPPV	475	Microcosting study (*Tables 18–21*)
GP telephone advice	21	Curtis 2007,[51] telephone consultation
GP surgery consultations	50	Curtis 2007,[51] clinic consultation lasting 17.2 minutes
GP home visits	55	Curtis 2007,[51] home visit lasting 23.4 minutes
Emergency department attendance	78	Reference costs 2007,[a] not leading to admission, category 1 investigation with category 1–2 treatment
Minor injuries unit	42	Reference costs 2007, not leading to admission, category 1 investigation with category 1–2 treatment
District nurse visits	24	Curtis 2007,[51] community nurse
Health visitor visits	36	Curtis 2007,[51] health visitor
Specialist cardiac nurse visits	58	Curtis 2007,[51] nurse advanced
Social worker visits	34	Curtis 2007,[51] social worker (adult) assuming 1-hour visit
Outpatient attendances (cardiology)	100	Reference costs 2007,[a] consultant-led follow-up attendance outpatient, face to face
Inpatient day:		
ICU	1353	
CCU	450	Reference costs 2007,[a] coronary care unit
HDU	659	
Other	260	Reference costs 2007,[a] non-elective heart failure without complications, cost per day (derived)
Prescriptions (per month)	5.77	Weighted average based on most frequently prescribed drugs at 1 month

ACPO, acute cardiogenic pulmonary oedema; CCU, coronary care unit; HDU, high dependency unit; ICU, intensive care unit; LUHT, Lothian University Hospitals NHS Trust.
a www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_074072.

TABLE 18 *Unit costs used in the microcosting study of the initial emergency department episode*

Resource	Unit	Cost (£) (2006/7)	Source
Consultant	Hour	175	Curtis 2007,[51] medical, per patient-related hour
Mid-grade	Hour	41	Curtis 2007,[51] SR, 56-hour week
Junior	Hour	32	Curtis 2007,[51] FHO2, 56-hour week
Senior nursing	Hour	69	Curtis 2007,[51] AfC7, hours of patient contact
Middle nursing	Hour	60	Curtis 2007,[51] AfC6, hours of patient contact
Lower nursing	Hour	40	Curtis 2007,[51] AfC5, hours of patient contact
Overheads	Hour	5.38	Sheffield Teaching Hospitals (STH)
Chest radiograph	Test	29.87	STH
Arterial blood gases	Test	9.47	STH
Full blood count	Test	3.13	STH
Urea and electrolytes	Test	2.46	STH
Blood sugars	Test	1.50	STH
Liver function test	Test	2.60	STH
Creatinine	Test	1.57	STH
Troponin	Test	6.21	STH
Thyroid	Test	3.37	STH
Other	Test	6.69	Average of all tests listed above
NIPPV machine	Patient	85.70[a]	

a Based on a discount rate of 3.5%, which produces an annuity factor of 4.67 (payable in advance), plus an annual workload of 130 patients of any diagnosis per annum (Lothian University Hospitals NHS Trust) and annual maintenance cost of 10% of the purchase price.

TABLE 19 *Non-invasive ventilation cost components*

Resource	Cost (£) (2006/7)	Source
Synchrony ST ventilator	6069	List price, 5-year life expectancy
Battery pack connector cable	29	5-year life expectancy
13.2V 10Ah portable battery pack	150	Per annum based on 2-year life expectancy (LUHT)
Fast charger for 9303	204	Per annum based on 1-year life expectancy (LUHT)
Face mask (various sizes)	52	Per patient, based on 1.5 masks per patient
Non-invasive ventilation disposable circuit	8	Per patient
Air inlet filter	27	Per month
Filter cap	9	Per month

LUHT, Lothian University Hospitals NHS Trust.

65.1% respectively. Reasons for not sending out questionnaires are outlined in *Table 22*.

There were no significant differences in the response rates between the three treatment arms (*Table 23*).

Table 24 shows resource use up to 6 months for each treatment group. There is weak evidence of differences in the mean number of inpatient days up to 6 months between the three groups ($p = 0.096$). A more noticeable difference is apparent in the number of primary and community

TABLE 20 *Non-invasive ventilation total cost*

Cost component	Cost over 5 years (£) (2006/7)
Machine	6098
Maintenance	3035
Replacement parts	3900
Consumables	39,033
Total	52,065
Cost per patient	86[a]

a Based on a discount rate of 3.5%, which produces an annuity factor of 4.67 (payable in advance), plus an annual workload of 130 patients of any diagnosis per annum (Lothian University Hospitals NHS Trust) and annual maintenance cost of 10% of the purchase price.

TABLE 21 *Breakdown of the initial emergency department episode unit costs for each study group (£)*

	Standard therapy ($n = 27$)	CPAP ($n = 21$)	NIPPV ($n = 20$)
Staff costs	186.08	237.74	282.54
Test costs	89.94	84.96	85.39
Machine costs	0.00	85.70	85.70
Emergency department overheads	21.52	21.52	21.52
Total costs:			
Mean	297.53	429.92	475.16
Minimum	142.70	197.41	284.39
Maximum	631.74	960.61	852.39

TABLE 22 *Reasons for not sending out questionnaires*

	1 month	3 months	6 months
Not sent questionnaire:			
Died	141	182	231
Refused delayed consent	49	49	49
Unable to give delayed consent	116	116	116
Requested no questionnaires	41	57	64
Unable to confirm patient status	17	24	22
Other reason	37	16	14
Sent questionnaire, no response	152	163	200
Sent questionnaire, response	516	462	373

care contacts, although this is not significant ($p = 0.059$).

Table 25 shows the costs up to 6 months for each treatment group. Once resource use is combined with unit costs there is no evidence of differences between the groups. Although this may appear contradictory given that there was some evidence of differences in the underlying resources, there are two reasons why this can occur. First, the inpatient and primary/community care categories represent aggregates of several different types of inpatient and primary/community care, each with different unit costs. Second, each of the categories in *Table 25* is based on a consistent sample size within each

TABLE 23 *Questionnaire response rates in the three treatment arms*

		Standard therapy	CPAP	NIPPV	*p*-value
1 month	Not sent	38.3%	38.7%	35.6%	0.854
	Responders	47.5%	48.3%	49.0%	
	Non-responders	14.2%	13.0%	15.4%	
3 months	Not sent	40.2%	43.1%	41.5%	0.606
	Responders	43.2%	41.0%	45.4%	
	Non-responders	16.7%	15.9%	13.2%	
6 months	Not sent	47.3%	46.8%	45.1%	0.964
	Responders	35.0%	34.1%	35.6%	
	Non-responders	17.8%	19.1%	19.3%	

TABLE 24 *Mean resource use up to 6 months by treatment group*

Resource item	Standard therapy	CPAP	NIPPV	*p*-value[a]
Inpatient days	17.6 ($n = 364$)	16.4 ($n = 338$)	19.5 ($n = 351$)	0.096
Outpatient attendances	2.5 ($n = 162$)	2.7 ($n = 152$)	2.8 ($n = 153$)	0.866
Primary/community contacts[b]	13.4 ($n = 162$)	27.2 ($n = 152$)	13.4 ($n = 153$)	0.045
Medication months[c]	26.0 ($n = 162$)	29.0 ($n = 152$)	30.0 ($n = 153$)	0.330
Days of informal care	33.4 ($n = 162$)	38.7 ($n = 152$)	40.3 ($n = 153$)	0.509

a *p*-values are for one-way analysis of variance.
b Includes GP telephone advice, GP surgery consultations, GP home visits, emergency department attendances, minor injuries unit attendances, district nurse visits, specialist cardiac nurse visits and social worker visits.
c Represents the number of months of medication, calculated as the number of individual medications multiplied by the number of months that each was prescribed for. The mean number of medications over the study period is one-sixth of the amount shown, i.e. 4.3, 4.8 and 5.1 for standard care, CPAP and NIPPV respectively.

TABLE 25 *Costs (£) up to 6 months by treatment group*

Resource item	Standard therapy ($n = 151$)	CPAP ($n = 138$)	NIPPV ($n = 140$)	*p*-value
Initial emergency department episode	298	430	475	N/A
Inpatients	4283 (225–14,768)	3961 (220–13,013)	4231 (260–14,454)	0.815
Outpatients	248 (0–1340)	274 (0–1303)	253 (0–1200)	0.894
Primary and community care	532 (0–1944)	867 (0–4943)	523 (0–1827)	0.080
Medications	146 (0–415)	159 (0–451)	168 (0–421)	0.486
Total cost at 6 months[a]	5507 (523–15,499)	5691 (650–16,855)	5649 (735–17,226)	0.949

a Cost of informal care excluded as it is outside the perspective of the study.
All values are means (5th and 95th percentiles), and *p*-values are for one-way analysis of variance.

group, whereas in *Table 24* different sample sizes are seen within each group.

When EQ-5D data are considered, and their associated estimate of QALYs, no significant differences are seen between the arms (*Table 26*). Mean values for patients are low, which is a product of the low quality of life of patients and the high mortality rate (which automatically generates utility values of zero).

TABLE 26 *EQ-5D data and quality-adjusted life-years (QALYs) at 6 months (with imputed missing data)*

	Standard therapy	CPAP	NIPPV	*p*-value
EQ-5D 1 month	0.464 (0.430–0.498)	0.483 (0.449–0.517)	0.500 (0.468–0.533)	0.325
EQ-5D 3 months	0.439 (0.404–0.473)	0.463 (0.426–0.499)	0.459 (0.425–0.493)	0.585
EQ-5D 6 months	0.421 (0.386–0.457)	0.448 (0.411–0.485)	0.411 (0.377–0.466)	0.344
QALYs	0.202 (0.187–0.217)	0.213 (0.197–0.228)	0.210 (0.195–0.224)	0.593

Lifetime costs and QALYs

When mortality for trial patients in months 4–6 was compared with age- and sex-matched general population figures, a relative risk of death of 3.967 was observed (*Table 27*). This was applied to annual mortality estimates for the general population (for which there are actuarial estimates of life expectancy) to estimate trial-specific age- and sex-matched life expectancies. The mean life expectancy for patients in the trial if they were alive at 6 months was 3.505 years (*Table 27*).

Compared with age- and sex-matched general population estimates, 6-month utilities of those patients alive were on average 0.165 lower. Subtracting this from the natural profile of utility seen in the general population and combining it with the trial life expectancies produces a mean estimate of 2.124 QALYs (*Table 27*). Mean costs in months 4–6 were £1341, which, when combined with trial life expectancy, produced a mean expected cost until death of £18,801 per patient surviving to 6 months (*Table 27*).

Four sets of data are available for the cost-effectiveness analysis: 6-month data without imputation ($n = 429$), 6-month data with imputation for missing values ($n = 1069$), lifetime data without imputation ($n = 429$) and lifetime data with imputation for missing values ($n = 1069$) (*Table 28*). Imputation appears to increase mean QALYs and reduce mean costs in the short term. This is because patients who died are over-represented in the data without imputation. These patients have high costs and low QALYs. Over the lifetime of patients, imputation produces similar costs to the complete case analysis, as the lower costs in the short term are offset by higher costs in the survivors.

Looking at the 6-month analysis without imputation, standard therapy is both the least costly and the least effective. Relative to standard therapy, CPAP and NIPPV produce ICERs of £92,000 per QALY and £10,900 per QALY respectively. Once these data are modelled to estimate lifetime cost-effectiveness, the ICERs change to £2600 and £86,400 per QALY for CPAP and NIPPV, respectively, relative to standard therapy.

After imputation a clear picture is seen, with standard therapy again being the least costly and least effective, and CPAP being the most effective and with similar costs to NIPPV. The estimates shown in *Table 28* do not show the sampling uncertainty around the ICERs for the unimputed analyses or the degree of dominance for the imputed analyses. Such uncertainty is illustrated in *Figures 13* and *14* for the lifetime analyses of unimputed and imputed data respectively.

TABLE 27 *Modelling parameters*

	All patients
Mean excess risk of death in months 4–6 relative to general population	3.967
Mean life expectancy at 6 months for patients alive at 6 months (years)[a]	3.505
Mean reduced utility relative to general population at 6 months	0.165
Mean lifetime QALY expectancy at 6 months for patients alive at 6 months[a]	2.124
Mean cost in months 4–6 for patients alive at 6 months (£)	1341
Mean lifetime cost at 6 months for patients alive at 6 months (£)[a]	18,801

a Discounted at 3.5% per annum.

TABLE 28 *Summary of total costs and quality-adjusted life-years (QALYs)*

	Costs			QALYs		
	Standard therapy	CPAP	NIPPV	Standard therapy	CPAP	NIPPV
At 6 months without data imputation[a]	5507	5691	5649	0.159	0.161	0.172
At 6 months with data imputation[b]	3023	3224	3208	0.202	0.213	0.210
Lifetime without data imputation[a]	15,659	16,115	16,350	1.329	1.503	1.337
Lifetime with data imputation[b]	15,764	17,525	17,021	1.597	1.841	1.707

a Sample sizes are 151, 138 and 140 for standard therapy, CPAP and NIPPV respectively.
b Sample sizes are 366, 346 and 357 for standard therapy, CPAP and NIPPV respectively.

For the complete case analysis the probability that CPAP is cost-effective at £20,000 per QALY is 71%, whereas for the analysis based on imputation using the last observation carried forward the probability that CPAP is cost-effective at £20,000 per QALY is 74%. Two additional analyses were undertaken to assess possible weakness in these estimates.

First, the estimation of lifetime costs and QALYs uses a fixed annual cost and utility, yet it would be better to characterise these as random variables. Consequently, these random variables were estimated using the distribution around the cost parameter in *Table 27* and the variability in the UK population norms of the EQ-5D. This has the effect of increasing the uncertainty around the results, with the probability that CPAP is cost-effective reducing to 63% (*Figure 15*).

Second, regression imputation of lifetime total costs was undertaken for patients with missing values using age and gender as covariates. This also had the effect of increasing the uncertainty around the cost-effectiveness estimates, with the probability that CPAP is cost-effective reducing to 62%.

Discussion

The methods used for the economic evaluation up to 6 months follow those routinely used for trial-based economic evaluations. However, to capture the longer-term effects we modelled the lifetime costs and outcomes. Although this is sometimes undertaken using a supplementary decision-analytic model, we took the decision to build this analysis directly on to the trial-based analysis. This should not produce significantly different values as the estimates of life expectancy and utilities are based on the same sources used for decision-analytic models.

The estimation of lifetime costs and effects does, however, change the results of the economic evaluation from a situation in which NIPPV appears the most cost-effective within the trial to one in which CPAP is the most cost-effective over the lifetime of the trial. Whether this demonstrates that modelling is a strength or a weakness is the source of some debate in the literature; however, the general opinion within health technology assessment is that modelling produces information that is more directly relevant to the decision-making context.

The results shown in *Figures 13* and *14*, which represent the approach identified in the analysis plan, each show one treatment to have a much higher probability of being cost-effective than its comparators. However, when alternative approaches are used that are more able to characterise the uncertainty around future costs, QALYs and imputed values, the probability that CPAP is the most cost-effective reduces to just over 60%. Further uncertainty could be added by using the distributions around the unit costs for emergency department treatment as estimated in the microcosting study; however, as uncertainty around all other unit costs is not typically incorporated into economic analyses, this was not pursued.

Finally, despite the modelling, some uncertainties inevitably remain, and future research could go some way to reducing these uncertainties. For example, another trial and meta-analysis could produce more precise estimates of mortality, or a cohort study could more precisely estimate the life expectancy of patients post discharge. A value of information analysis could use the economic evaluation as a starting point and produce estimates of areas in which future research would be of greatest value to policy-makers. Such an analysis is beyond the scope of this report.

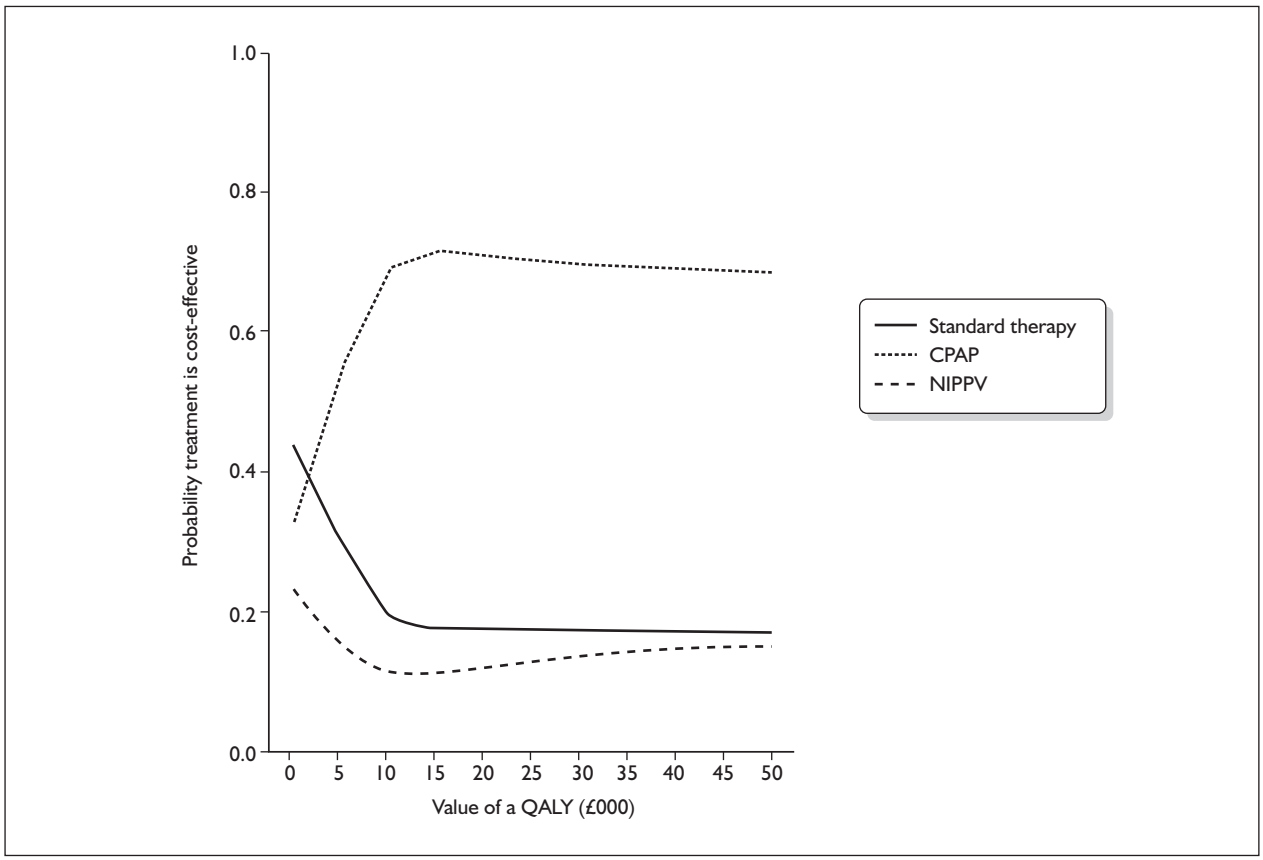

FIGURE 13 *Cost-effectiveness acceptability curves for lifetime costs and quality-adjusted life-years (QALYs) without imputation.*

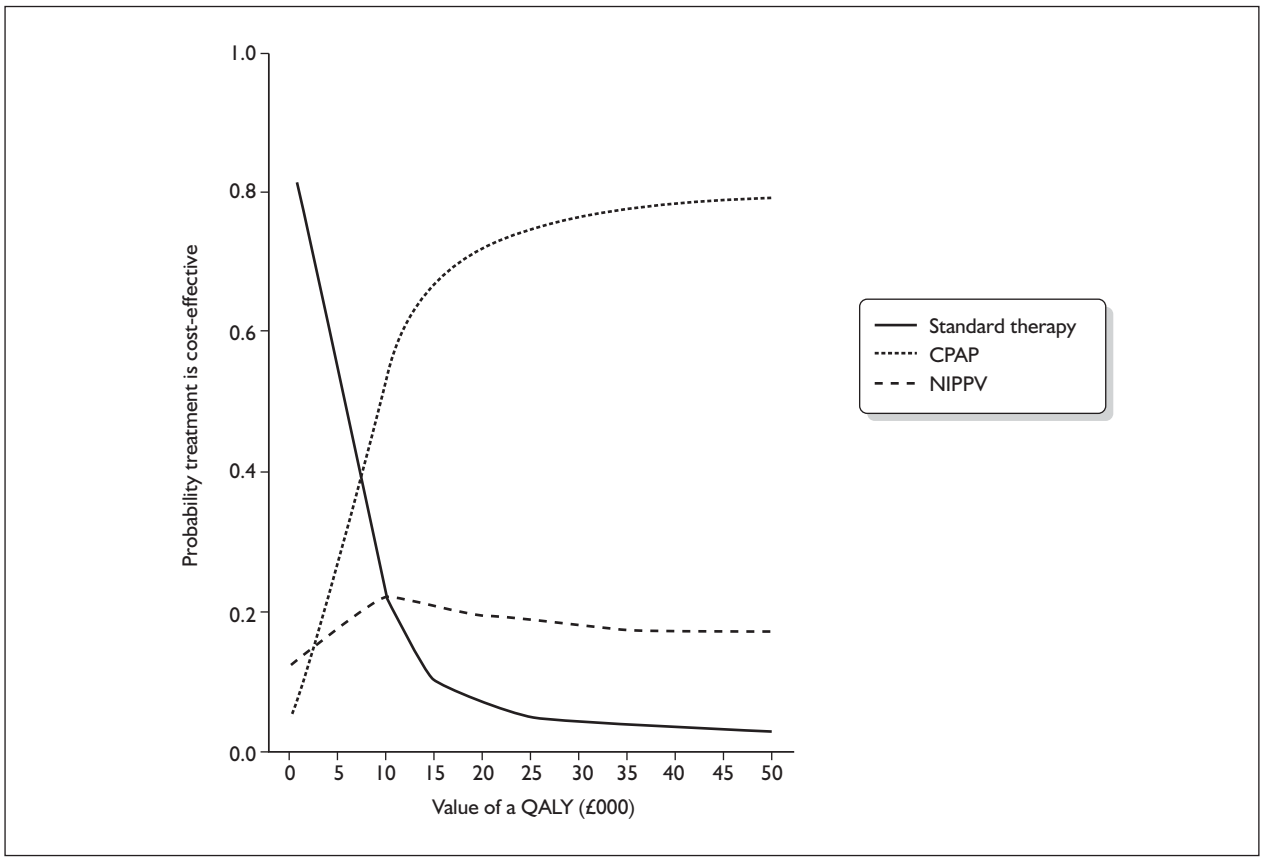

FIGURE 14 *Cost-effectiveness acceptability curves for lifetime costs and quality-adjusted life-years (QALYs) with imputation.*

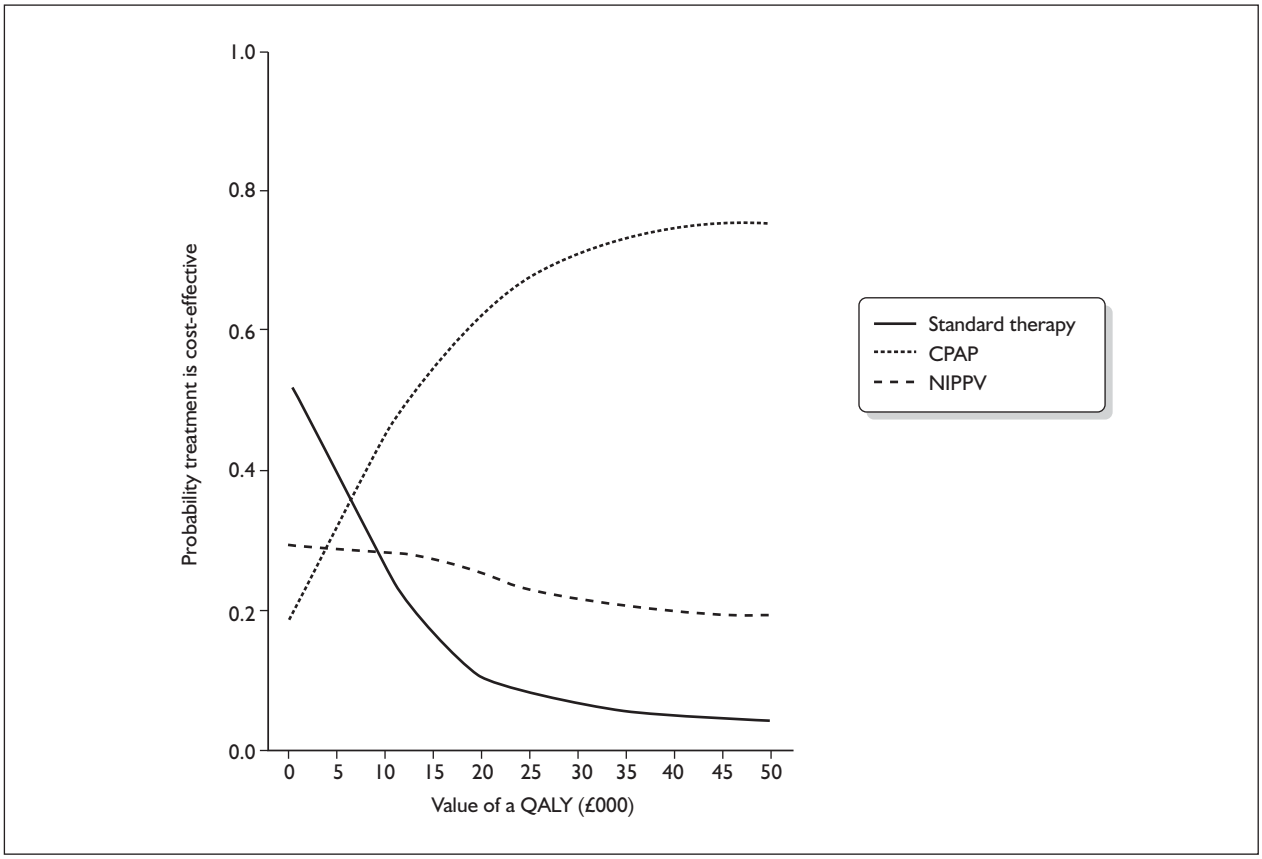

FIGURE 15 *Cost-effectiveness acceptability curves for lifetime costs and quality-adjusted life-years (QALYs) with imputation and specification of future costs and utilities as random variables.*

Chapter 5
Discussion

The 3CPO trial has shown no difference in short- or long-term mortality rates between standard oxygen therapy and non-invasive ventilation treatments in patients presenting to emergency departments with severe acute cardiogenic pulmonary oedema. In addition, there were no major differences in treatment efficacy or safety between the two non-invasive ventilation modalities of CPAP and NIPPV. This was despite early improvements in symptoms and surrogate measures of disease severity.

Specifically, there was no demonstrable difference in any primary or secondary outcome for the comparison between non-invasive ventilation and standard oxygen therapy other than for breathlessness measured by visual analogue scale, physiology at 1 hour (pulse rate) and arterial gas exchange parameters at 1 hour (pH and pCO_2). There was no clear difference in any primary or secondary outcome for the comparison between CPAP and NIPPV. Moreover, despite continuing concerns[11,40] regarding the potential for an increase in MI rates in patients treated with NIPPV, the 3CPO trial has confirmed the safety of the intervention.

Interpretation of principal trial findings

These results are contrary to the findings of a number of recent meta-analyses[11–16] despite similar improvements in physiological and gas exchange variables. These meta-analyses and systematic reviews of immediate treatment with non-invasive ventilation in patients with acute cardiogenic pulmonary oedema have reported up to a 47% reduction in mortality.[11] The 3CPO trial was adequately powered to assess this question and recruited more patients than the total combined experience of these analyses and reviews.

There are a number of potential reasons why the 3CPO trial findings do not support the results of previous small randomised controlled trials[21–36] and the conclusions drawn from multiple recent meta-analyses.[11–16]

Patient population

The population of patients recruited to the 3CPO trial may be different from those recruited to the 25 or so small randomised controlled trials previously reported. In particular, there may be differences in age, severity of illness, comorbidities and underlying mechanisms of heart failure. We believe this to be unlikely for the following reasons.

Based on previous studies we applied strict inclusion and exclusion criteria and targeted the group of patients most likely to benefit from non-invasive ventilation, i.e. those with respiratory distress and acidosis. These criteria are particularly relevant as this group is most likely to benefit from the additional mechanistic advantages of NIPPV.[52] Indeed, the recent trial by Nava and colleagues[28] showed a reduction in intubation rates only in a hypercapnic subgroup. The baseline characteristics and event rates in the non-invasive ventilation arms were comparable to those in previous studies and demonstrate that we recruited patients with severe disease. There was no evidence of patient selection bias with identical 7-day mortality in non-recruited patients (9.2%). Indeed, this is further supported by the excellent recruitment rates of eligible patients compared with those previously reported. In keeping with previous analyses[11] there was no interaction between treatment intervention and disease severity, suggesting that those with milder disease did not obscure potential benefits in the sickest patients. We therefore believe that we have robustly targeted and assessed the correct patient population.

Our trial mortality rate was higher than those in registry data (6.7%, EHFS II;[53] 4%, ADHERE registry[54]) and participants were older and predominantly female. These discrepancies in mortality and patient characteristics are likely to relate to differing study populations. Acute heart failure registries include all patients with decompensated heart failure rather than only those with severe acute pulmonary oedema. Indeed, in the EHFS registry, only 16% of patients had a qualifying diagnosis of acute pulmonary oedema.

Our patient age, male–female ratio and co-morbidities were similar to those in previous

primary trials, with a mean age between 75 and 80 years, a female preponderance and highly comparable co-morbidities such as hypertension, ischaemic heart disease, diabetes, chronic heart failure and chronic obstructive pulmonary disease.[23,26–28,33,36]

It could be argued that a significant number of patients, given the age and sex characteristics of recruited patients, had relatively preserved systolic function, so-called diastolic heart failure, and may be more amenable to rapid vasodilatation. As echocardiography was not routinely performed as part of the trial protocol we cannot refute this; however, the rate of MI is consistent with rates in previous trials. Indeed, even using the more traditional WHO criteria for MI definition the index rates for MI are considerably higher than those in a recent large trial undertaken by Moritz and colleagues[33] from France. Despite this, in-hospital mortality is identical between the two trials.

We therefore believe that patients recruited to the 3CPO trial are broadly similar to those in previous studies.

Influence of co-treatments

Although not mandated, the 3CPO trial recommended a set of co-treatments for recruited patients (Appendix 1). This specifically included buccal and intravenous nitrates. Approximately 90% of patients received this intervention. It is possible that the cardiovascular beneficial effects of non-invasive ventilation in acute cardiogenic pulmonary oedema[18–20,50] have been masked by another treatment working (in particular nitrates) by the same mechanism, i.e. a reduction in preload and afterload.[55–57] Indeed, Crane[56] identified prehospital nitrate as being the only factor associated with improved mortality in a UK observational study of patients with acute cardiogenic pulmonary oedema. Co-treatments in previous small trials have often been incompletely characterised and documented. It is therefore unclear whether there is consistency in these treatments across trials.

Ineffective delivery of trial intervention

It could be argued that one reason why this trial failed to reveal a difference in mortality was that the intervention was ineffectively delivered. Over 80% of sites had previous experience of non-invasive ventilation before the trial starting. There was a comprehensive training programme for all centres to ensure operator competence and consistency throughout the trial. We used a readily applied portable ventilator that allowed both modalities of ventilation to be delivered as well as a tolerance for leaks around the face mask of up to 50 l/min. Although unable to measure the inspired oxygen concentration, the circuit delivers an oxygen concentration of up to 60%. There was a drop in oxygen saturations and partial pressure of arterial oxygen with both CPAP and NIPPV at 1 hour but this was modest and of questionable clinical relevance. Indeed, in contrast to standard oxygen therapy there were no treatment failures due to worsening hypoxia in these intervention arms. Mean pressures for both CPAP (10 cmH_2O) and NIPPV (14/7 cmH_2O) are highly comparable to those in previous studies.[10,11] Mean times of delivery of the interventions were a little over 2 hours, suggesting that the patients were physiologically and symptomatically significantly better within this short time frame. There was crossover between interventions in all three arms of the trial and these were analysed on an intention to treat basis; there were differing reasons for crossover with respiratory distress and hypoxia being more likely in the control arm and lack of patient tolerance being more likely in the two intervention arms. If these patients are removed from the primary outcome analysis there remains no significant difference between groups. We therefore do not believe that the crossovers influenced the trial's principal conclusions.

The intervention (non-invasive ventilation) is ineffective

Was the trial intervention ineffective? Irrespective of treatment modality, non-invasive ventilation produced a more rapid improvement in respiratory distress and metabolic abnormalities. These findings are consistent with the majority of previous studies investigating the benefits of CPAP and NIPPV,[21–36] and confirm the successful, appropriate delivery of the therapeutic intervention in our trial. We acknowledge that improvement in breathlessness (0.7 on a 10-point scale) was modest,[58] but this is a crude measure of breathlessness and, when tolerated, non-invasive ventilation was associated with fewer treatment failures due to respiratory distress. Finally, despite the theoretical additional benefits of NIPPV,[52] we observed no differences in therapeutic efficacy between the two treatment modalities.

Interpretation of previous data is inaccurate

Another potential reason for the differences in findings is that the meta-analyses may be wrong. Recent meta-analyses and systematic reviews have been composed of numerous randomised clinical trials. However, individual trials were composed of small treatment group sizes that varied between 9 and 65 patients, with recruitment rates of only 10–30% (compare with 62% randomised in the 3CPO trial). In the meta-analyses the small total number of outcome events was well below the recommended threshold of 200[59] and this limits the generalisability of their findings. There is real concern of reporting, publication and recruitment bias in individual published studies that will be compounded by pooled analysis. The discrepancy between our results in the setting of a large randomised controlled trial and previous pooled data is not unique, and the limitations of meta-analysis are well reported.[60]

Differing thresholds for endotracheal intubation and critical care admission

Previous trials have indicated that the physiological improvement seen with non-invasive ventilation is translated into a reduction in tracheal intubation rates.[10,11] Pooled data from the meta-analysis by Peter and colleagues[11] suggest that six patients need to be treated with CPAP and seven with NIPPV to avoid one patient being intubated and mechanically ventilated. In contrast, the 3CPO trial found no benefit of non-invasive ventilation in reducing intubation rates and this may reflect the relatively low intubation rates we observed. Reasons for this are unclear but may reflect the differing patient populations, concomitant therapies and thresholds for intubation and mechanical ventilation across different countries, clinical environments and time periods. Intubation rates in the standard therapy arms vary from 35–65% in initial trials[22,23] to 5–7% for recent trials in emergency department settings,[26,36] despite a similar severity of illness, in-hospital mortality and length of hospital stay. Intubation rates in the intervention arms have also fallen considerably over time with some initial trials reporting rates of up to 35% whereas recent reports have consistently suggested rates of around 5%. Indeed, a recent large trial[33] from France has reported a 3% intubation rate, which is almost identical to that in the 3CPO trial. Given that the present and previous trials were by necessity 'open', there is real concern of treatment bias with a differing threshold for intervention according to treatment allocation. For example, patients on standard oxygen therapy may be more likely to undergo intubation than those already gaining the apparent benefit of non-invasive ventilation. Additionally, clinicians may persevere with patients slow to improve with non-invasive ventilation if they believe in its efficacy. It is important to note that intubation does not correlate with mortality in our trial or severity of illness in those previously reported.[11]

Safety and side effects

Mehta and colleagues[21] prematurely terminated their trial comparing CPAP with NIPPV because of the concerns of an increase in MI rate in the NIPPV arm. A subsequent study by Bellone and colleagues[31] did not replicate this finding and demonstrated no effect of NIPPV on MI rate. The systematic review by Peter and colleagues[11] reported a weak relationship between the delivery of NIPPV and an increase in MI rate. This finding was largely the result of the weighting of Mehta's study[21] in the pooled data. The 3CPO trial has shown that there is no relationship between MI rate and the application of either CPAP or NIPPV. Similar to previous reports, side effects directly related to the interventions were rare and resulted in no significant reported consequences.

Implications for practice

Non-invasive ventilation is widely used in UK emergency departments for patients with severe acute cardiogenic pulmonary oedema.[37] Given the results of this trial we believe that CPAP should be the non-invasive ventilation modality of choice, as NIPPV provides no additional benefit over CPAP and CPAP equipment is less complex and less expensive. In addition, a number of simple systems allow the delivery of 100% oxygen. Clearly if a department already has equipment in use or is using NIPPV for other clinical conditions such as chronic obstructive pulmonary disease then this will influence the decision as to the ventilation mode and equipment type used for pulmonary oedema. Lastly, we believe that in the majority of patients medical therapy should be instigated as the primary treatment of severe acute cardiogenic pulmonary oedema and non-invasive ventilation reserved for those patients who have significant respiratory distress and failure or those not improving with standard medical therapy.

Chapter 6
Conclusions

Non-invasive ventilatory support delivered by either CPAP or NIPPV safely provides earlier improvement and resolution of breathlessness, respiratory distress and metabolic abnormalities. However, this does not translate into improved survival. We recommend that non-invasive ventilation (CPAP or NIPPV) should be considered as adjunctive therapy in patients with severe acute cardiogenic pulmonary oedema in the presence of severe respiratory distress or when there is a failure to improve with pharmacological therapy.

Acknowledgements

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Recruiting sites, clinical leads and patients recruited

Royal Infirmary of Edinburgh, Alasdair Gray ($n = 161$); Southern General Hospital, Glasgow, Phil Munro ($n = 23$); Ninewells Hospital, Dundee, Neil Nichol ($n = 21$); Crosshouse Hospital, Crawford McGuffie ($n = 50$); Hairmyres Hospital, Kilmarnock, John Keaney ($n = 28$); Northern General Hospital, Sheffield, Steve Goodacre ($n = 136$); York Hospital, Steve Crane ($n = 63$); St James's University Hospital, Leeds, Steve Bush ($n = 56$); Leeds General Hospital, Taj Hassan

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Alasdair Gray contributed to the conception and design of the study, interpretation of the data, first draft and revising of the report, and final approval. Steve Goodacre contributed to the conception and design of the study, analysis and interpretation of the data, drafting of the economics section, revising of the report and final approval. David Newby contributed to the conception and design of the study, interpretation of the data, revising of the report and final approval. Moyra Masson contributed to the design of the study, the first draft of the methods section and final approval. Fiona Sampson contributed to the analysis and interpretation of the data, the first draft of the methods section and final approval. Simon Dixon contributed to the analysis and interpretation of the health economic data, the first draft of the methods section and final approval. Steven Crane contributed to the conception and design of the study, revising of the report and final approval. Mark Elliott contributed to the conception and design of the study, revising of the report and final approval. Jon Nicholl contributed to the conception and design of the study, analysis and interpretation of the data, drafting of the economics section, revising of the report and final approval.

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Gray A, Elliott MW, Goodacre S, Newby DE, Sampson F, Nicholl J, *et al*. Non-invasive ventilation in patients with acute cardiogenic pulmonary oedema: the 3CPO trial (a multicentre randomised controlled trial). *Thorax* 2007;**62**(Suppl.):A8.

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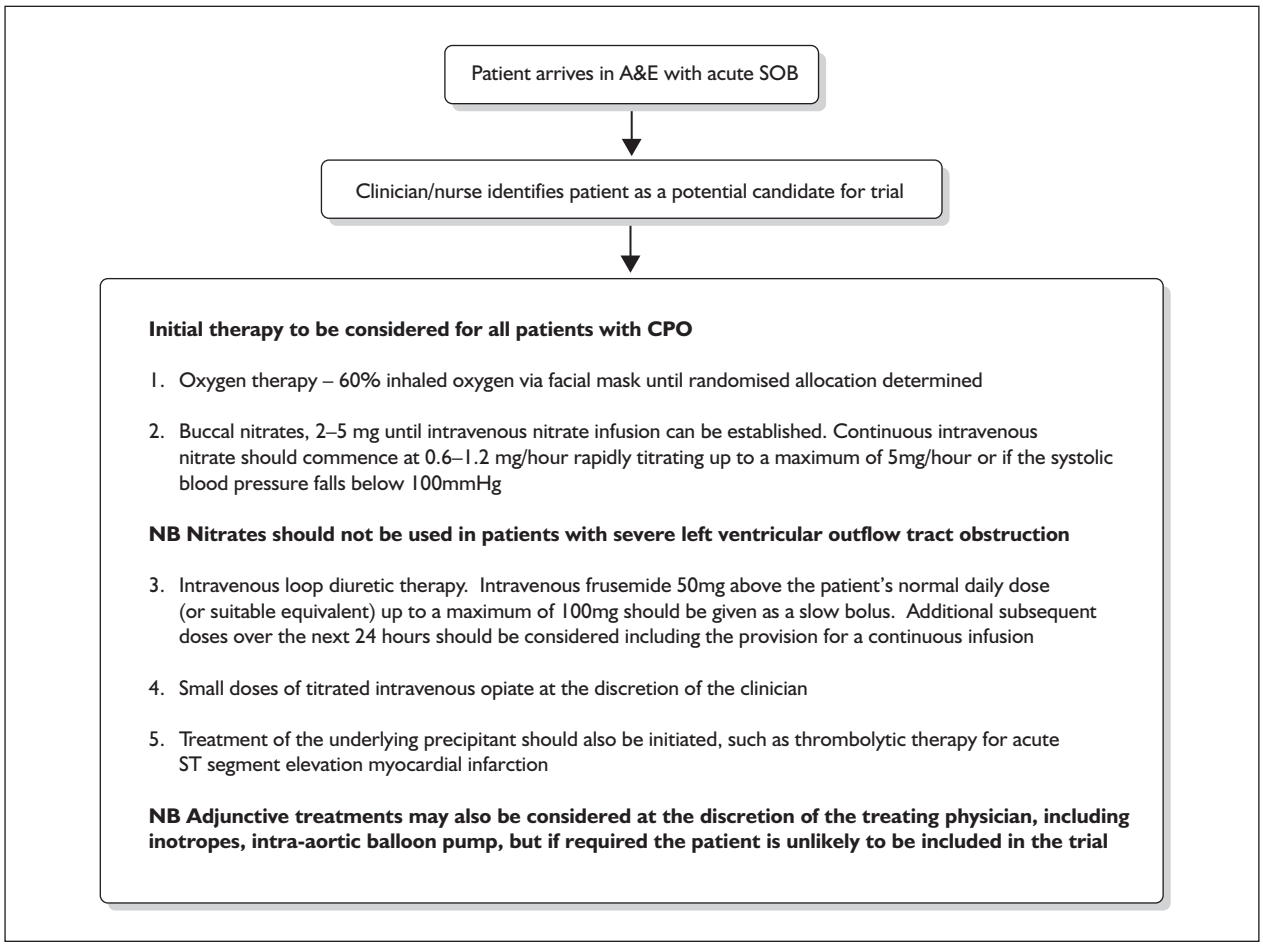
Appendix 1
Treatment guidelines

Cardiogenic pulmonary oedema



A&E, emergency department; SOB, shortness of breath.

Appendix 2

Patient information sheet

PATIENT INFORMATION SHEET FOR 3CPO STUDY

You are being invited to take part in a RESEARCH study because you have acute heart failure, which has left fluid on your lungs. **Please read the following information carefully**.

Participation is entirely VOLUNTARY, and you need not give a reason for declining to participate.

If you do decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive.

You will be involved in the research for around **2 hours** in the emergency department (A&E) whilst the early treatment of your condition is going on.

In this study, we are comparing three different ways of delivering oxygen because we do not know which one is best. ALL patients in this study will receive the usual drug treatment for acute heart failure and oxygen.

However, the oxygen may be delivered in one of THREE different ways:

1. by a simple face mask
2. by a tight-fitting face mask connected to a breathing machine (ventilator) that is delivering oxygen at one continuous pressure (CPAP)
3. by a tight-fitting face mask connected to a breathing machine (ventilator) that is delivering oxygen at a higher pressure when you breathe in than when you breathe out (NIPPV).

These treatments will be selected entirely at random by a computer (i.e. by chance). There is a one in three chance of receiving any of the treatments. Patients in the three groups will then be receiving oxygen in three different ways and these will be compared.

There *may* be some **side effects** to treatment with the non-invasive ventilator machine and these include:

1. minor skin damage to the face due to the tight-fitting mask
2. vomiting
3. a drop in blood pressure
4. claustrophobia.

We plan to monitor all patients very closely so that all of these problems can be quickly identified and treated.

All information that is collected about you during the course of this study will be kept strictly confidential. Any information about you that leaves the hospital will have your name and address separated from it so that you cannot be identified from it and will only be used by individuals directly involved in the research project.

The study has been approved by a Multicentre Research Ethics Committee and reviewed by the Local Research Ethics Committee.

Further information can be obtained from:

THANK YOU VERY MUCH IN ADVANCE FOR YOUR HELP WITH THIS STUDY

Appendix 3

Relative information sheet

RELATIVES INFORMATION SHEET FOR 3CPO STUDY

(Is non-invasive ventilation effective in patients with acute heart failure?)

Your relative is being invited to take part in a RESEARCH study. However, as your relative is unwell, you are being asked to read the following information carefully, to discuss it with others and to ask us if you would like further information about the study. Thank you for taking the time to read this. You will be given this information sheet to keep.

Why has my relative been chosen as a potential study patient?

Your relative has been chosen as a potential study patient because he/she has heart failure, which has left fluid on his/her lungs. We aim to study 1200 such patients in a nationwide research study.

What is the purpose of the study?

To find out if a machine designed to deliver oxygen under pressure into a face mask improves the condition of patients with fluid on the lungs caused by heart failure. These machines are known to help patients with other breathing problems (such as emphysema).

What treatment might my relative receive?

In this study, we are comparing three different ways of delivering oxygen because we do not know which one is best. **ALL** patients in this study will receive the usual drug treatment for acute heart failure and oxygen.

However, the oxygen may be delivered in one of THREE different ways:

1. by a simple face mask
2. by a tight-fitting face mask connected to a breathing machine (ventilator) that is delivering oxygen at one continuous pressure (CPAP)
3. by a tight-fitting face mask connected to a breathing machine (ventilator) that is delivering oxygen at a higher pressure when you breathe in than when you breathe out (NIPPV).

These treatments will be selected entirely at random by a computer (i.e. by chance). There is a one in three chance of receiving any of the treatments. Patients in the three groups will then be receiving oxygen in three different ways and these will be compared.

Are there any side effects to treatment?

There ***may*** be some **side effects** to treatment and these include:

1. minor skin damage to the face due to the tight-fitting mask
2. vomiting
3. a drop in blood pressure
4. claustrophobia.

We plan to monitor all patients very closely so that all of these problems can be quickly identified and treated.

How long will the research study last?

If, in your opinion, your relative WOULD consent to be enrolled, he/she will be involved in the research for around 2 hours in the emergency department (A&E) whilst the early treatment of his/her condition is going on. No additional tests or clinic visits will be required. However, we will send your relative a questionnaire by post at 1, 3 and 6 months after the date of their hospital admission to help us assess how well they are. We may telephone your relative at home to remind them to fill in these questionnaires.

Why is my opinion important?

You are being asked to read this sheet so that you are aware that we are conducting the research and that we would like to enrol your relative in the study. As you know your relative much better than we do, we would like you to give your opinion as to whether or not your relative would agree to take part in the study if he/she was well enough to make an informed choice.

YOUR RELATIVE IS THE *ONLY* PERSON WHO MAY GIVE *CONSENT* TO BE INVOLVED IN A RESEARCH STUDY OF THIS KIND. As his/her relative, you are being asked *only* for your opinion as to whether or not they would consent to be enrolled if they were well enough to do so. This will help us to ensure that we do not enrol someone who would feel very unhappy about taking part in the research. The doctor looking after your relative (and NOT you) is taking responsibility for all the treatments that your relative receives and will at all times ensure that those treatments are in his/her best interests.

What happens to my relative if I say 'No'?

If you do NOT think that your relative would agree to take part OR you yourself feel unable to give your opinion, then your relative will NOT be enrolled into the study. This will not affect the standard of care your relative receives, and all the subsequent treatments given will be undertaken by the doctor in his/her best interests.

What happens if I say 'Yes' but my relative is subsequently unhappy to continue to take part in the study?

As your relative is too ill to provide informed consent for this research himself or herself,

we will talk to them at a later date (when their health has improved) about the research project and to obtain their personal consent to continued participation in it. A member of the research team will speak to your relative about the research to ensure that they are happy to continue to be part of the project. Your relative will then be free to provide their own informed consent to take part in the research or to withdraw from the project if they so wish. This will not affect the standard of care they receive or their legal rights.

If your relative decides to withdraw from the study after initially being enrolled then only the information already collected about your relative will be used in any subsequent data analysis for the purposes of the research. It will, however, remain in their medical records to assist in the treatment of their medical condition.

How will my relative's confidentiality be maintained?

Your relatives medical records may be inspected for the purpose of analysing the results. All information that is collected about them during the course of this study will be kept strictly confidential. Any information about them that leaves the hospital will have their name and address separated from it so that they cannot be identified. We hope to publish the results of this study in medical journals, but their name will not be entered in any publication.

Other information

Sometimes, during the course of a research project, new information becomes available about the treatment being studied. If this happens your research doctor will tell your relative about it and discuss whether they want to continue in the study. If you or they decide to withdraw, the research doctor will make arrangements for your relative's care to continue. An updated consent form will be provided.

If your relative is harmed during the course of this research project there are no special compensation arrangements. If they are harmed because of someone's negligence you or they may have grounds for legal action but may have to pay for it. If you or your relative wish to complain about any aspect of the way they have been approached or treated during the course of this study, the normal NHS complaints mechanisms should be available to you.

We hope that all the treatments will help your relative. However, this cannot be guaranteed. The information we get from this study may help us to improve the treatment of future patients.

The study has been approved by a Multicentre Research Ethics Committee and reviewed by the Local Research Ethics Committee.

Further information can be obtained from:

THANK YOU VERY MUCH IN ADVANCE FOR YOUR HELP WITH THIS STUDY

Appendix 4

Patient consent form

ISRCTN: 07448447 Study number: ☐☐☐☐☐ Form number: ☐☐☐☐

PATIENT CONSENT FORM FOR 3CPO STUDY

(Is non-invasive ventilation effective in patients with acute heart failure?)

Lead Researcher:

	Please tick to confirm
I have read the information sheet for the above study	◯
I have had the opportunity to ask questions about the study and to discuss it with family and friends	◯
I understand the purpose of the study and how I will be involved	◯
I understand, and accept, that if I take part in the study I may not gain direct personal benefit from it	◯
I understand and accept that, as explained in the information sheet the treatment I am given may have some side effects	◯
I understand that all information collected in the study will be held in confidence and that, if published or presented, all my personal details will be removed	◯
I give permission for the researchers and responsible individuals from regulatory authorities to have access to my medical notes and other routine NHS data sources when this is relevant to my taking part in the research	◯
I confirm that I will be taking part in the study of my own free will, and I understand that I may withdraw from it, at any time and for any reason, without my medical care or my legal rights being affected	◯
I agree to take part in the above study	◯

Patient name: _____ Date: ___/ ___/ ___ Signature: _____

Verbal consent only ◯ **Please tick box and clinician and witness sign**

Person taking consent: _____ Date: ___/ ___/ ___ Signature: _____

Witness name: _____ Date: ___/ ___/ ___ Signature: _____

PRINTED NAME AND SIGNATURE FOR ALL ABOVE

Appendix 5

Relative opinion form

ISRCTN:
07448447

Study number: ☐☐☐☐☐ Form number: ☐☐☐☐

RELATIVE OPINION FORM FOR 3CPO STUDY

(Is non-invasive ventilation effective in patients with acute heart failure?)

Lead Researcher:

	Please tick to confirm
I have read the information sheet for the above study.	◯
The patient's name is: _____	
My name is: _____	
Please state relationship to patient: _____	
I have had the opportunity to ask questions about the study and to discuss it with family and friends.	◯
I understand the purpose of the study and how my relative will be involved.	◯
I understand that, if my relative takes part in the study they may not gain direct personal benefit from it.	◯
I understand that, as explained in the information sheet, the treatment my relative is given may have some side effects.	◯
I understand that all information collected in the study will be held in confidence and that, if published or presented, all personal details regarding my relative will be removed.	◯
I give permission for the researchers and responsible individuals from regulatory authorities to have access to medical notes and other routine NHS data sources when this is relevant to my relative taking part in the research.	◯
I understand that I may change my opinion, at any time and for any reason, without my relative's medical care or legal rights being affected.	◯
In my opinion my relative would consent to being enrolled in the study if he/she was well enough to make an informed decision. I understand that the doctor looking after my relative is responsible for all the treatment that he/she receives and will ensure his/her best interests at all times.	◯

Relative name: _____ Date: ___/ ___/ ___ Signature: _____

Person taking consent: _____ Date: ___/ ___/ ___ Signature: _____

Witness name: _____ Date: ___/ ___/ ___ Signature: _____

PRINTED NAME AND SIGNATURE FOR ALL ABOVE

Appendix 6

Retrospective information sheet

ISRCTN: 07448447 Study number: ☐☐☐☐☐ Form number: ☐☐☐☐

PATIENT RETROSPECTIVE INFORMATION SHEET FOR 3CPO STUDY
(Is non-invasive ventilation effective in patients with acute heart failure?)

You were recently admitted to hospital with acute heart failure, which had left fluid on your lungs. We are currently undertaking a research project, looking at the use of a new ventilator machine in this condition. As you were very unwell at the time, it was impossible to inform you fully about the research study and to expect you to understand this information. Your doctor therefore carried out your treatment in your best interests and your initial enrolment in the research study may also have been discussed with an important relative. Now that you are feeling better it is very important that you are made aware of what the research study is all about and that we ensure you are happy to continue to take part in it. You are being asked to read the following information carefully, to discuss it with others and to ask us if you would like further information about the study. You will be given this information sheet to keep and asked to sign a consent form if you wish to continue to take part in the research. Thank you for taking the time to read this.

Why was I chosen as a potential study patient*?*

You were chosen as a potential study patient because you had heart failure, which had left fluid on your lungs. We aim to study 1200 such patients in a nationwide research study.

What is the purpose of the study?

To find out if a machine designed to deliver oxygen under pressure into a facemask, improves the condition of patients with fluid on the lungs caused by heart failure. These machines are known to help patients with other breathing problems (such as emphysema).

What treatment did I receive?

In this study, we are comparing three different ways of delivering oxygen because we do not know which one is best. **ALL** patients in this study receive the usual drug treatment for acute heart failure and oxygen.
However, the oxygen may be delivered in one of THREE different ways:

1) **by a simple face mask**
2) **by a tight fitting face mask connected to a breathing machine (ventilator) which is delivering oxygen at one continuous pressure (CPAP)**
3) **by a tight fitting face mask connected to a breathing machine (ventilator) which is delivering oxygen at a higher pressure when you breathe in than when you breathe out (NIPPV).**

These treatments are being selected entirely at random by a computer, (i.e. by chance). There was a one in three chance of receiving either of the treatments. Patients in the three groups will then have received oxygen in three different ways and these will be compared.

The treatment that you received was_____

Were there any side effects to treatment in my case?

There ***may*** be some **side effects** to treatment and these include:

1) minor skin damage to the face due to the tight fitting mask

2) vomiting

3) a drop in blood pressure

4) claustrophobia

You suffered the following side effects _____

How long will the research study last?

You were involved in the research for around two hours in the emergency department (A&E) whilst the early treatment of your condition was going on. No additional tests or clinic visits will be required. We will send you a questionnaire by post at 1, 3 and 6 months after the date of your hospital admission to help us assess how well you are. We may telephone you at home to remind you to fill in these questionnaires.

What happens if I am unhappy to continue to take part in the study?

You are free to provide informed consent to continue to take part in the research or to withdraw from the project, if you so wish. This will not affect the standard of care you receive or your legal rights.

If you decide to withdraw from the study, after initially being enrolled, then only the information already collected about you will be used in any subsequent data analysis for the purposes of the research. It will, however, remain in your medical records to assist in the treatment of your medical condition.

How will my confidentiality be maintained?

Your medical records and other routine NHS data sources may be inspected for the purpose of analysing the results. All information that is collected about you during the course of this study will be kept strictly confidential. Any information about you that leaves the hospital will have your name and address separated from it so that you cannot be identified. We hope to publish the results of this study in medical journals, but your name will not be entered in any publication.

Other information

Sometimes, during the course of a research project, new information becomes available about the treatment being studied. If this happens, your research nurse will tell you about it and discuss whether you want to continue in the study. If you or decide to withdraw, the research nurse will make arrangements for your care to continue. An updated consent form will be provided.

If you were harmed during the course of this research project, there are no special compensation arrangements. If you were harmed due to someone's negligence you may have grounds for legal action but may have to pay for it. If you or your relative wish to complain about any aspect of the way they have been approached or treated during the course of this study, the normal NHS complaints mechanisms should be available to you.

We hope that all the treatments have helped you. The information we get from this study may help us to improve the treatment of future patients.

The study has been approved by a Multicentre Research Ethics Committee and reviewed by the Local Research Ethics Committee.

Further information can be obtained from:

THANK YOU VERY MUCH IN ADVANCE FOR YOUR HELP WITH THIS STUDY

Appendix 7

Retrospective consent form

ISRCTN: 07448447

Study number: ☐☐☐☐☐ Form number: ☐☐☐☐

PATIENT RETROSPECTIVE CONSENT FORM FOR 3CPO STUDY

(Is non-invasive ventilation effective in patients with acute heart failure?)

Lead Researcher:

	Please tick to confirm
I have read the information sheet for the above study	◯
I have had the opportunity to ask questions about the study and to discuss it with family and friends	◯
I understand the purpose of the study, how I have already been involved, and how I will be involved in the future	◯
I understand, and accept, that if I continue to take part in the study I may not gain direct personal benefit from it	◯
I understand that all information collected in the study will be held in confidence and that, if published or presented, all my personal details will be removed	◯
I give permission for the researchers and responsible individuals from regulatory authorities to have access to my medical notes and other routine NHS data sources when this is relevant to my taking part in the research	◯
I confirm that I will be taking part in the study of my own free will, and I understand that I may withdraw from it, at any time and for any reason, without my medical care or my legal rights being affected	◯
I agree to take part in the above study	◯

Patient name: _____ Date: ___/ ___/ ___ Signature: _____

Person taking consent: _____ Date: ___/ ___/ ___ Signature: _____

Witness name: _____ Date: ___/ ___/ ___ Signature: _____

PRINTED NAME AND SIGNATURE FOR ALL ABOVE

Appendix 8

Patient satisfaction with care questionnaire

ISRCTN: 07448447 Study number: ☐☐☐☐☐ Form number: ☐☐☐☐

PATIENT SATISFACTION WITH CARE FOR 3CPO STUDY

We are interested in your honest opinions, whether they are positive or negative, regarding the care you received when you arrived at the hospital. Your answers will be confidential and will not be seen by any of the doctors or nurses who are caring for you.

Please answer all of the questions. We also welcome your comments and suggestions. Thank you very much for your help, which is much appreciated.

Thinking about your treatment in the emergency department (A&E), how would you rate the following? (Please circle **one** number on each line)

1) The thoroughness of examinations and accuracy of diagnosis

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

2) The skill, experience and training of hospital staff

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

3) The thoroughness of treatment

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

4) Explanations given to you about medical procedures and tests

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

5) Attention given to what you have to say

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

6) Advice you got about ways to avoid illness and stay healthy

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

7) Friendliness and courtesy shown to you by hospital staff

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

8) Personal interest in you and your medical problems

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

9) Respect shown to you, and attention to your privacy

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

10) Reassurance and support offered to you by hospital staff

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

11) Amount of time the hospital staff gave you

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

12) Overall, how satisfied are you with the service you received?

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

13) We would value any other comments that you may have regarding your care. Please document these in the space below:

Appendix 9

Main data collection form

ISRCTN: 07448447 Study number: ☐☐☐☐☐ Form number: ☐☐☐☐

3CPO: – MAIN DATA COLLECTION FORM

Before completing this form, please ensure you have filled in the study number above, and copied the form number (top right) onto the patient recruitment form.

Please complete ALL details on this page and page two and as much as you can on pages three and four. The Research Nurse will complete the rest of the form.

Section A: Intervention details

1. Which intervention was started?

Please tick one only – if more than one treatment was started, please tick the first treatment started and provide details of further interventions in Q4.

1. Standard treatment ◯
2. NIPPV ◯
3. CPAP ◯

2. Treatment start time: __ __ : __ __ Treatment finish time: __ __ : __ __

3. What was the final level for:

(i.e. highest level of tolerance within 2 hours)

CPAP: _____ cmH_2O

NIPPV: ____ / ____ cmH_2O

4. Was the allocated treatment completed? Yes ◯ No ◯

If not, why not?
- Patient did not tolerate treatment ◯
- Worsening blood gases ◯
- Increasing respiratory distress ◯
- Other, please specify ◯

_____

5. If more than one intervention was started, please state which treatment was started after failure of intervention above.
- Standard treatment ◯
- CPAP ◯
- NIPPV ◯
- Intubation ◯
- Other (please specify) ◯

_____

PLEASE COMPLETE ALL PAPERWORK AND CONTINUE WITH 1 & 2 HOUR OBSERVATIONS EVEN IF PATIENT DOES NOT CONTINUE RANDOMISED TREATMENT

ISRCTN: 07448447

Study number: | | | | | | Form number: | | | | |

Section A: Symptoms prior to admission

Has the patient had symptoms suggestive of MI during 12 hours before hospital attendance? Yes ◯ No ◯

Section B: Your observations

		Baseline (on considering eligibility)	One hour (after randomisation)	Two hours (after randomisation)
i.	Pulse rate	_____	_____	_____
ii.	Blood pressure	_____	_____	_____
iii.	Respiratory rate	_____	_____	_____
iv.	Oxygen saturation (%)	_____	_____	_____
v.	Inspired O_2 concentration (O_2 l /min)	_____	_____	_____
vi.	Arterial pH	_____	_____	
vii.	Arterial pO_2 (KPa)	_____	_____	
viii.	Arterial pCO_2 (KPa)	_____	_____	
ix.	Standard bicarbonate (mmol/l)	_____	_____	
x.	Breathlessness score (0–10). Patient assessed – ask the patient	_____	_____	0=not breathless, 10=breathless X = too breathless to respond
xi.	Glasgow Coma Score verbal	____ / 5	____ / 5	
xii.	Glasgow Coma Score eye-opening	____ / 4	____ / 4	
xiii.	Glasgow Coma Score motor	____ / 6	____ / 6	

Section C: Your treatment

Treatment	Administered?	If yes, which drug?	Dose? (if infusion, max rate of infusion attained in ml per hour within first 2 hours)	Route?
Nitrates	Yes ◯ No ◯	_____	_____	_____
Opiates	Yes ◯ No ◯	_____	_____	_____
Diuretics	Yes ◯ No ◯	_____	_____	_____

Other medications and interventions (please specify):

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Section D: Past medical history

Please tick 'yes' or 'no' for all questions.

Myocardial infarction	Yes	◯	No	◯
Angina	Yes	◯	No	◯
Percutaneous coronary revascularisation	Yes	◯	No	◯
Coronary artery bypass graft	Yes	◯	No	◯
Coronary heart disease (not otherwise specified)	Yes	◯	No	◯
Heart failure	Yes	◯	No	◯
Valvular cardiac disease	Yes	◯	No	◯
Any other cardiac disease	Yes	◯	No	◯

If OTHER, please specify: _____

Chronic obstructive pulmonary disease	Yes	◯	No	◯
Cerebrovascular accident	Yes	◯	No	◯
Peripheral vascular disease	Yes	◯	No	◯
Hypertension	Yes	◯	No	◯
Diabetes	Yes	◯	No	◯
Hypercholesterolaemia	Yes	◯	No	◯
Family history of premature CHD	Yes	◯	No	◯
Current smoker	Yes	◯	No	◯

If YES, number of cigarettes per day: _____

Ex-smoker	Yes	◯	No	◯
Any other chronic disabling illness	Yes	◯	No	◯

If OTHER, please specify: _____

Patient's usual MRC breathlessness score (1–5 – see below) _____

MRC breathlessness score

1 I only get breathless with strenuous exercise

2 I get short of breath when hurrying on the level or up a slight hill

3 I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level

4 I stop for breath after walking 100 yards or after a few minutes on the level

5 I am too breathless to leave the house

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Section E: Pre-hospital treatment

Treatment	Administered?	If yes, which drug?	Dose?	Route?
Nitrates	Yes ◯ No ◯	_____	_____	_____
Opiates	Yes ◯ No ◯	_____	_____	_____
Diuretics	Yes ◯ No ◯	_____	_____	_____

Inspired oxygen concentration: _____ litres per minute

Other medication and interventions (please specify): _____

Section F: Regular medication

Please tick 'yes' or 'no' for all questions.

Inhaled beta agonists	Yes ◯	No ◯
Inhaled steroids	Yes ◯	No ◯
Oral theophylline/aminophylline	Yes ◯	No ◯
Oral steroids	Yes ◯	No ◯
Sublingual GTN	Yes ◯	No ◯
Diuretic	Yes ◯	No ◯
ACE inhibitor	Yes ◯	No ◯
Beta-blocker	Yes ◯	No ◯
Calcium-channel antagonist	Yes ◯	No ◯
Oral nitrates	Yes ◯	No ◯
Aspirin	Yes ◯	No ◯
Clopidogrel	Yes ◯	No ◯
Warfarin	Yes ◯	No ◯
Nicorandil	Yes ◯	No ◯
Aldosterone receptor antagonist	Yes ◯	No ◯
Other	Yes ◯	No ◯

If OTHER, please specify: _____

Please leave the form in the trial folder for the research nurse to complete.

Thank you.

The 3CPO Study *ISRCTN: 07448447* Study number: ☐☐☐☐☐ Form number: ☐☐☐☐

Sections G J to be completed by the research nurse only.

Section G: Complications within 24 hours *not specifically related to CPAP or NIPPV*

Details of complications specifically related to CPAP or NIPPV should not be recorded here, but in section H below.

Vomiting	Yes	◯	No	◯
Gastric aspiration	Yes	◯	No	◯
Hypotension (systolic <90)	Yes	◯	No	◯
Arrhythmia requiring treatment	Yes	◯	No	◯
Pneumothorax	Yes	◯	No	◯
Progressive respiratory distress	Yes	◯	No	◯
Cardiorespiratory arrest	Yes	◯	No	◯
Any other complication	Yes	◯	No	◯

Please give details of <u>all</u> complications:

Section H: CPAP/NIPPV details and details of side effects within 24 hours if continuing beyond 2 hours

Length of time on active intervention (CPAP/NIPPV) (hours):
<6 hours ◯ 6–11 hours ◯ 12–17 hours ◯ 18–23 hours ◯ 24 hours + ◯

Treatment tolerated?	Yes	◯	No	◯

If NO please give further details:

Side effects due to active intervention (CPAP / NIPPV):

Facial skin necrosis	Yes	◯	No	◯
Face discomfort	Yes	◯	No	◯
Increased breathing discomfort	Yes	◯	No	◯
Other side effect	Yes	◯	No	◯

If OTHER please specify:

ISRCTN: 07448447 Study number: ☐☐☐☐☐ Form number: ☐☐☐☐

Section I: Seven-day outcome data

Did the patient receive a treatment they were not allocated to receive (other than any treatment specified on page 1)? Yes ◯ No ◯

If patient recommenced on NIV please answer the following three questions. If multiple discrete episodes of NIV please only consider the first episode after trial intervention.

If YES, please state which treatment: CPAP ◯ NIPPV ◯

For how many hours after attendance was treatment administered? _____ hours

Length of time on treatment? _____ hours

<6 hours ◯ 6–11 hours ◯ 12–17 hours ◯ 18–23 hours ◯ 24 hours + ◯

Has the patient undergone endotracheal intubation? Yes ◯ No ◯

If YES, how many hours after attendance was intubation performed? _____ hours

Is the patient alive at seven days? Yes ◯ No ◯

If NO, please record: Date of death: __ / __ / __ Cause of death:

Over the last 7 days, has the patient suffered any symptoms suggestive of MI after initial hospital attendance? Yes ◯ No ◯

If YES, how long after attendance was the worst pain? _____ hours / days

Please attach and label the following ECGs:

1. Any ECG recorded prior to this admission
2. The first recorded ECG
3. Any subsequent ECG recorded within two hours
4. Any subsequent ECG recorded between two and 24 hours
5. Any subsequent ECG recorded between 24 hours and seven days

Please detail results of any biochemical cardiac markers since admission:

Test used (name)	Sample no	Date of sample	Time of sample	Result
_____	1	__ / __ / __	____ : ____	_____
_____	2	__ / __ / __	____ : ____	_____
_____	3	__ / __ / __	____ : ____	_____
_____	4	__ / __ / __	____ : ____	_____
_____	5	__ / __ / __	____ : ____	_____
_____	6	__ / __ / __	____ : ____	_____
_____	7	__ / __ / __	____ : ____	_____
_____	8	__ / __ / __	____ : ____	_____
_____	9	__ / __ / __	____ : ____	_____
_____	10	__ / __ / __	____ : ____	_____

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Section J: 30-day outcome data

Is the patient alive at 30 days? Yes ◯ No ◯

If NO, please record: Date of death: __ / __ / __ Cause of death:

Location at 30 days Hospital ◯ Home ◯ Other ◯

If HOME, please check that the address is the same as that recorded on the front sheet

If OTHER, please specify: Address

Postcode

Total length of hospital stay: _____ days

Number of ward days spent in hospital: _____ days

Number of days spent on ITU: _____ days

Number of days spent on CCU: _____ days

Number of days spent on HDU _____ days

Has the patient undergone:	PTCA or coronary stenting?	Yes ◯	No ◯
	Coronary artery bypass grafting?	Yes ◯	No ◯
	Any other cardiac surgery?	Yes ◯	No ◯
	If OTHER please specify: _____		
	Echocardiogram	Yes ◯	No ◯
	Thallium scanning	Yes ◯	No ◯
Has the patient received:	Intravenous thrombolysis	Yes ◯	No ◯
	Glycoprotein IIB/IIIA inhibitors	Yes ◯	No ◯
	Cardiac inotropes	Yes ◯	No ◯
	Intra-aortic balloon pump	Yes ◯	No ◯

Appendix 10

Recruitment form

ISRCTN 07448447

Study number: ☐☐☐☐☐ Form number: ☐☐☐☐

3CPO: – PATIENT RECRUITMENT FORM – ***please follow trial algorithm on 3CPO poster***

Section A: Your details and patient details *(for patient, please complete or attach sticky label)*

Patient's name: Your name:

Date of birth: __ / __ / __ Sex: Date: __ / __ / __ Time:

Address: Hospital:

Hospital case note number:

Postcode Tel no: A&E number:

Section B: Inclusion criteria

Please tick YES or NO for each of the following statements: ***YES*** NO

i. Is the patient aged over sixteen? ○ ○
ii. Does the patient have shortness of breath? ○ ○
iii. Does the patient have bilateral crackles on chest auscultation? ○ ○
iv. Does the patient's chest X-ray show pulmonary oedema? ○ ○
v. Is the patient's arterial pH less than 7.35? (H^+ > 45 nmol) ○ ○
vi. Is the patient's respiratory rate greater than 20 breaths per minute? ○ ○
vii. Is the patient responsive to verbal stimuli? ○ ○
viii. Does the patient require immediate advanced life support (defibrillation or endotracheal intubation) or thrombolysis? ○ ○
ix. Is the CPAP/NIPPV equipment available to use? ○ ○
x. Is the patient known to have been included in the 3CPO study previously? ○ ○

If you have ticked <u>any</u> of the shaded boxes, <u>the patient is not eligible</u>. Please go to section E below.

Section C. Consent – if you have ticked *all* the unshaded boxes:

Please seek patient's consent or relative's assent using appropriate form. Then tick one of the following:

The patient has provided written, informed consent (form attached) ○
I have witnessed the patient provide verbal consent (form attached) ○
The patient's relative has provided written assent (form attached) ○

If consent or assent has been obtained, telephone the randomisation hotline and complete the form
0113 343 4928

Neither consent nor assent to study inclusion could be obtained ○
Please state reason _____

Do <u>not</u> randomise patient. Go to section E

Section D: Trial details - PLEASE COMPLETE THIS SECTION

Study number (provided by the randomisation hotline): _____

Treatment allocation: (please tick one) **1. Standard treatment** ○ **2. NIPPV** ○ **3.CPAP** ○

Unable to get through to randomisation hotline ○

Section E: Patient status

Not eligible ◯ Eligible, not consented ◯ Eligible, consented, entered into trial ◯ Unable to randomise ◯

Signed: _____ Date: __ / __ / ___

Research nurse to complete GP details: GP name: Tel no:

Address: Postcode:

When completed, please place in the trial folder. If the patient has been entered into the trial, please now complete the data collection form.

Health Technology Assessment reports published to date

Volume 1, 1997

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By Richards DM, Deeks JJ, Sheldon TA, Shaffer JL.

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A review by Selley S, Donovan J, Faulkner A, Coast J, Gillatt D.

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The diagnosis, management, treatment and costs of prostate cancer in England and Wales.
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A review by Murray J, Cuckle H, Taylor G, Hewison J.

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A review of near patient testing in primary care.
By Hobbs FDR, Delaney BC, Fitzmaurice DA, Wilson S, Hyde CJ, Thorpe GH, *et al*.

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Neonatal screening for inborn errors of metabolism: cost, yield and outcome.
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We look forward to hearing from you.

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