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The NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), based at the University of Southampton, manages evaluation research programmes and activities for the NIHR

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Title of the project

Systematic review and cost-effectiveness analysis of pre-hospital non-invasive ventilation for acute respiratory failure

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Project protocol:

Research objectives

1. To estimate the effect of pre-hospital non invasive ventilation (NIV) upon survival in patients with acute respiratory failure.
2. To estimate the incremental cost per quality-adjusted life year (QALY) gained by providing pre-hospital NIV instead of standard care.
3. To estimate the expected value of information associated with reducing uncertainty around key parameters.

Existing research

Acute respiratory failure occurs when disease of the heart or lungs lead to failure to maintain adequate blood oxygen levels (hypoxia) or increased blood carbon dioxide levels (hypercapnia). Pneumonia , chronic obstructive pulmonary disease (COPD), acute lower respiratory infection and heart failure are the main causes of acute respiratory failure and were together responsible for 379,731 hospital admissions in England in 2009-10. Some 53,578 (14%) of these patients died within 30 days of admission [1], typically after developing acute respiratory failure.

The definitive treatment of acute respiratory failure depends upon the underlying cause, but patients often require treatment in the ambulance whilst en route to hospital (pre-hospital treatment). At this point it is difficult to accurately determine the underlying cause, so pre-hospital treatment of acute respiratory failure often follows a common pathway rather than being specific to the underlying cause. Around 10% of medical admissions to hospital via emergency ambulance arrive at hospital with hypoxia (peripheral oxygen saturation below 92%) despite pre-hospital oxygen therapy [2]. This equates to around 300 patients per day in the NHS. The risk of death in patients with respiratory problems increases markedly with distance travelled to hospital, from 10% with distances below 10km to 20% with distances over 20km [3]. This is probably because hospital treatments for acute hypoxaemic respiratory failure, particularly those involving respiratory support, are not routinely available in the pre-hospital setting.

NIV involves providing respiratory support through a tight-fitting mask around the patient's mouth and nose. It may take the form of continuous positive airway pressure (CPAP) or non-invasive positive pressure ventilation (NIPPV). CPAP is simpler to use and thus more suitable for pre-hospital care. Acute respiratory failure is often associated with elevated carbon dioxide levels and acidosis, in addition to hypoxia. In patients with chronic respiratory disease oxygen therapy may reduce respiratory drive and worsen hypercapnia and thus outcome. NIV can improve gas exchange and outcome in these circumstances.

Extensive research has evaluated the in-hospital role of NIV for various causes of acute respiratory failure. Meta-analysis of in-hospital trials for COPD [4] has shown that NIPPV is associated with reduced mortality (relative risk 0.41; 95% confidence interval 0.26 to 0.64) and need for intubation (relative risk 0.42; 0.31 to 0.59). Systematic review of in-hospital trials of NIV for pneumonia has shown equivocal effects, especially in patients without COPD [5]. Several meta-analyses of CPAP and NIPPV in acute cardiogenic pulmonary oedema (ACPO) have shown reduced mortality and intubation rates [6, 7]. The 3CPO trial [8] was

published after the meta-analyses and showed that CPAP and NIPPV improved physiological parameters and symptoms of breathlessness in ACPO but did not reduce mortality or intubation rates.

Less research has been undertaken evaluating the pre-hospital use of NIV. We have undertaken a scoping review of NIV for acute respiratory failure and have identified six published randomised trials, outlined in the table below [9-14]. A search of ClinicalTrials.gov identified one other trial that had been planned and registered, but then abandoned due to difficulties in training investigators [15]. There appeared to be no other trials in progress.

First author, date & location	Study population	Intervention	Control	Primary outcome	Main results
Plaisance [9] 2007 France	ACPO (N=124)	Early CPAP provided by medical responders	Late CPAP provided in hospital	Patient reported dyspnoea score	Early CPAP was associated with improved breathlessness score (p=0.0003), reduced intubation rates (9.5% v 26.2%, p=0.01) and reduced mortality (3.2% v 13.1%, p=0.05)
Weitz [10] 2007 Germany	ACPO (N=23)	NIV provided by medical responders	Standard oxygen therapy	Change in oxygen saturation	NIV was associated with higher oxygen saturation on hospital arrival (97.3 v 89.5, P=0.002) but no significant difference in mortality (7.8% v 10%, p=1.0)
Thompson [11] 2008 Canada	Severe respiratory distress (N=71)	CPAP provided by paramedics	Standard oxygen therapy	Intubation rate	CPAP was associated with reduced intubation rates (20% v 50%, p=0.014) and weak evidence of reduced mortality (14.3% v 35.3%, p=0.064)
Frontin [12] 2011 France	ACPO (N=124)	CPAP provided by medical responders	Standard medical therapy	Treatment success*	CPAP was associated with no difference in treatment success (35.5% v 31.7%, p=0.65) or mortality (10.0% v 11.3%, p=0.52)
Roessler [13] 2011 Germany	Acute respiratory failure (N=51)	NIV provided by emergency physician	Standard medical therapy	Not specified	NIV was associated with no difference in rate of invasive ventilation (4% v 24%, P=0.104) or mortality (4% v 8%, P=1.0)
Ducros [14] 2011 France	ACPO (N=207)	CPAP provided by medical responders	Standard medical therapy	Treatment success**	CPAP was associated with increased treatment success (79% v 63%, p=0.01) but no difference in hospital mortality (8% v 9%, p=0.9)

*Defined as respiratory rate < 25/min and oxygen saturation > 90% at one hour

** Defined as the absence of death, intubation criteria, persistence of either all inclusion criteria or circulatory failure at the second hour or their reappearance before 48 h

The published trials were small (N=23 to 207) and used a variety of interventions, personnel, study populations and primary outcomes. None of the trials were powered to detect differences in mortality. Results were mixed with four reporting a significant difference in the primary outcome [9-11, 14], one reporting no significant difference [12] and one not

specifying the primary outcome [13]. In all the trials mortality was lower in the intervention arm but this was only statistically significant in one trial [9].

Two non-randomised trials have compared ambulance services providing NIV to those without. Craven et al [16] evaluated 62 patients with heart failure transported by two services, one with and one without NIPPV, and found that oxygen saturations increased quicker with NIPPV but there was no significant difference in mortality or intubation rate. Hubble et al [17] compared 120 patients with ACPO in a service providing CPAP to 95 in a service providing standard oxygen therapy. CPAP was associated with lower intubation rate, lower mortality and improved physiology. A cost-effectiveness model based on this study [18] showed that provision of CPAP in a typical emergency medical service would cost \$490 per life saved and was cost-effective. However, this analysis used several favourable assumptions and may have underestimated the true costs of delivering pre-hospital CPAP.

A number of other studies have reported the use of NIV in case series of patients with ACPO or other causes of respiratory failure [19-24] and one non-randomised study treatment with helmet CPAP and medical therapy to helmet CPAP alone [25]. These studies help to demonstrate the feasibility of pre-hospital NIV but cannot determine effectiveness.

Two systematic reviews have evaluated the role of pre-hospital NIV for ACPO [26,27]. Neither included all the randomised trials that have now been published and neither undertook meta-analysis.

Joint Royal Colleges Ambulance Liaison Committee (JRCALC) guidelines [28] recommend considering assisted ventilation for patients with peripheral oxygen saturation below 90% despite high flow oxygen therapy. Specific guidance for pulmonary oedema recommends using CPAP if training and equipment allow. To our knowledge, pre-hospital use of CPAP is currently limited to critical care paramedics in a few specific settings, such as the South East Coast Ambulance Service. However, interest in providing CPAP is growing. In the United States the National Association of Emergency Medical Services Physicians (NAEMSP) stated that NIPPV is an important treatment modality for the pre-hospital management of acute dyspnoea [29]. In the United Kingdom it was identified among research priorities by the recent 999 EMS Research Forum [30].

With around 16,000 paramedics and 5,500 ambulance vehicles in England, widespread adoption of NIV into paramedic practice would require substantial resources for training and equipment. Pre-hospital treatment of acute respiratory failure also has substantial knock-on costs for the health service. Patients with life-threatening respiratory illness often require prolonged hospital stay and/or critical care involvement due to the requirement for ventilatory support. Inadequate or inappropriate initial management can result in the need for respiratory support and critical care admission. Conversely, the appropriate use of early intervention can reduce the need for intubation and ventilation, thus reducing critical care costs.

Pre-hospital NIV thus has potential to reduce mortality in acute respiratory failure, but widespread provision of pre-hospital NIV will require substantial resources, training and reorganisation. It is currently not clear whether existing evidence justifies widespread use of

pre-hospital NIV. It is also not clear what further evidence would be required to reduce uncertainty and help decision-making. Undertaking a large randomised trial of pre-hospital NIV would reduce uncertainty but it is not clear whether the current evidence base justifies such a substantial undertaking.

Research methods

We will use the following methods to estimate the effectiveness and cost-effectiveness of pre-hospital NIV for acute respiratory failure and identify priorities for future research:

1. Systematic review of randomised trials
2. Meta-analysis of randomised trials, including individual patient data (IPD) meta-analysis if appropriate data are available
3. Decision analysis modelling of cost-effectiveness
4. Value of information analysis

Systematic review

A systematic review will be undertaken in accordance with guidelines published by the Centre for Reviews and Dissemination [31] and the protocol will be registered with the PROSPERO register [32]. The main purpose of the systematic review is to identify randomised trials that evaluate the effectiveness of pre-hospital NIV in patients with acute respiratory failure. The systematic review will also be used to identify data sources for the economic model, such as existing economic analyses, observational studies and non-randomised studies of pre-hospital NIV.

Search strategy

Relevant studies will be identified through electronic searches of key electronic databases including MEDLINE, EMBASE and all databases in the Cochrane Library (including the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials and NHS Economic Evaluations Database). References will also be located through review of reference lists for relevant articles and through use of citation search facilities through the Web of Knowledge. In addition systematic searches of trial registries and the Internet using the Google search engine will be used to identify unpublished materials and work in progress. Key authors and professional and academic research groups will also be contacted and asked for unpublished material.

Review strategy

We will select studies that fulfil the following criteria:

1. Design : Randomised (individual or cluster) or quasi-randomised controlled trials
2. Population: Patients presenting to the emergency services with acute respiratory failure due to any cause or no specified cause
3. Intervention: Pre-hospital NIV, defined as ventilatory support, provided before arrival at hospital, and delivered to a spontaneously breathing patient without airway intervention
4. Control: Any alternative to pre-hospital NIV, including standard oxygen therapy, delayed NIV or in-hospital NIV
5. Outcome: Any measure of patient health, clinical status or resource use

Non-randomised, observational or modelling studies that fulfil criteria 2, 3 and 5 will be retrieved, reported descriptively and, if appropriate, used to develop the economic model, but will not be systematically sought or subject to meta-analysis.

We will exclude studies where NIV is not used as part of acute treatment by the emergency care system, for example where NIV is used as home treatment for chronic respiratory problems.

The inclusion of potentially relevant articles will be undertaken using a two-step process:

1. All titles will be examined for inclusion by one reviewer. Any citations that clearly do not meet the inclusion criteria (i.e. non-human, unrelated to acute respiratory failure) will be excluded.
2. All abstracts and full text articles will be examined independently by two reviewers. The decisions will be coded and recorded on a Reference Manager database by the Project Manager.

Data extraction

Data extraction will be undertaken independently with discrepancies being discussed by the data extractors. Those that cannot be resolved at this stage will be referred to the rest of the project team. The following standardised data will be extracted from each eligible study: population characteristics (age, gender, diagnosis, co-morbidities, baseline physiology), intervention (system used, pressure(s) used, duration of treatment), comparison (any use of NIV, supplemental oxygen), practitioners providing intervention (paramedic or physician, 1st or 2nd responder), specified co-treatments, primary outcome measure and results of key outcomes (primary outcome, mortality, intubation rate, measures of breathlessness and respiratory function).

We will contact the authors of all randomised trials to clarify details, obtain missing data and request individual patient data (IPD) for meta-analysis.

Quality assessment

The methodological quality of each included study will be assessed using the criteria proposed by Verhagen et al for randomised controlled trials [33].

Data synthesis

The primary outcome for meta-analysis will be short-term survival (e.g. to 30 days or hospital discharge, depending upon the primary data). Meta-analysis of secondary outcomes, such as intubation rate, physiological variables or measures of respiratory function, will be undertaken if adequate data are retrieved. Sensitivity analysis will explore potential sources of heterogeneity, in particular whether CPAP or NIPPV was used and whether pre-hospital providers were paramedics or physicians.

The controls in the studies identified in the scoping study were:

- Standard oxygen therapy
- Standard medical therapy
- Late CPAP provided in hospital

The interventions evaluated in the studies identified in the scoping study were:

- Early CPAP provided by medical responders
- CPAP provided by paramedics
- CPAP provided by medical responders
- NIV provided by medical responders
- NIV provided by emergency physician

In order to make inferences about the individual interventions, we will assume that the three controls are equivalent. In making this assumption, the evidence base would form a network of evidence that would allow us to conduct a network meta-analysis. In the event that further studies that allow us to form a network of evidence, particularly about late CPAP provided in hospital, we will not make this assumption. We will also use clinical judgement to determine whether this is a reasonable assumption.

We will then conduct a network meta-analysis to assess the relative effect of each treatment against “standard therapy”. We will also consider combining certain interventions in order to strengthen inferences if the evidence suggests that they are effectively equivalent.

We will use a random effects meta-analysis to allow for heterogeneity between trials. Of interest would be the effect of age, baseline oxygen saturation and the underlying condition. In principle, we would consider performing a meta-regression to evaluate the impact of these factors on the heterogeneity between studies. However, this may not be possible if the number of studies that are identified is small. In addition, it is well known that meta-regression can be misleading as a consequence of the ecological fallacy. Where possible, we will obtain individual patient-level data to enable the effects of covariates of interest to be evaluated.

The primary outcome of measure, mortality, is typically recorded as a binary outcome and results presented as the response rate at some time-point e.g. 30 days. However, the time-points may vary across trials. In this case, we will (1) contact the authors and seek to obtain data at a standard time-point, or (2) if there is evidence to suggest that longer follow-up results in additional events, we will use suitable statistical models that allow us to model the time-varying rates.

A key secondary outcome measure of interest is the intubation rate, which is also recorded as a binary outcome. Again, we will either seek to obtain consistently reported data or use statistical models that allow us to model the potential effects of time.

The network meta-analysis models will be fitted using a Bayesian framework. Results from the network meta-analysis will be used to characterise the uncertainty about inputs to the decision analytic model by drawing samples from the joint posterior distributions.

Decision analysis modelling

Economic analysis will be undertaken from a health and social care perspective over the lifetime of the patient. We will develop a decision-analytic model to estimate the cost-effectiveness of pre-hospital NIV in terms of cost per QALY gained compared to standard

care. The model will compare the management of a theoretical population with acute respiratory failure attended by emergency ambulances providing pre-hospital NIV to management by ambulances without pre-hospital NIV. Estimates of effectiveness from the systematic review will determine the proportion of patients surviving to 30 days or hospital discharge.

We will use the systematic review to identify estimates of health utility and survival after treatment with pre-hospital NIV for acute respiratory failure, including non-randomised or observational studies. We will also identify utility estimates used in previous economic analyses of pre-hospital NIV retrieved by the systematic review. In addition, we will use utility estimates from two data sources of our own:

1. The 3CPO Trial: This HTA-funded trial evaluated in-hospital NIV in 1069 patients with acute cardiogenic pulmonary oedema. Survival was measured until 1-5 years after hospital admission and EQ-5D was measured at 1, 3 and 6 months after admission [34,35]
2. The DAVROS study: This MRC-funded observational study measured survival and surveyed EQ-5D in 5760 patients 30 days after emergency hospital admission, including 1060 with diseases of the respiratory system [36]

We will use studies identified in the literature review, routine data sources, expert opinion and contact with manufacturers of NIV equipment to estimate the costs of providing pre-hospital NIV (including equipping ambulances, maintaining equipment and training paramedics), costs of inpatient care and lifetime costs of care after hospital admission with acute respiratory failure. We will also use our contacts with ambulance services to identify whether any are currently using prehospital NIV and, if so, whether they are able to provide any routine data or audit data describing its use.

In addition, SchARR is currently undertaking cost-effectiveness modelling relating to COPD and CHF on other projects. Firstly, an HTA project commissioned by the NIHR is being undertaken within the NICE Technology Appraisal contract examining the cost-effectiveness of telehealth for CHF (<http://www.hta.ac.uk/project/2351.asp>). Secondly, the Mainstreaming Assistive Living Technologies (MALT) Project which is funded by the Technology Strategy Board is also ongoing which will be developing a COPD model in addition to amending the HTA CHF model (<http://www.fastuk.org/research/projview.php?id=1703>). Whilst these models are not completely relevant for this study, they should be readily adaptable to allow the estimation of post-hospitalisation costs, quality of life and life-expectancy for these two patient groups (which comprise the majority of acute respiratory failure patients).

The conceptual model structure for this project is likely to be relatively simple as the main outcome measures will be based on the percentage of survivors and the assumed quality of life for patients that achieve short-term survival. The authors are very familiar with Markov and Decision Tree models, although have published using discrete event simulation and meta-models should the data collected be more suited to these modelling approaches.

The main output from the model will be an estimate of the incremental cost per QALY gained by providing NIV compared to standard care for acute respiratory failure. We will

also use net benefit analysis and cost-effectiveness acceptability curves to demonstrate the probability that NIV will be cost-effective at varying levels of willingness to pay for health gain. Further modelling will take an ambulance service perspective to estimate the additional costs incurred by establishing and providing pre-hospital NIV, and the lives saved and QALYs gained across the population served by a typical ambulance service.

The expected value of perfect information (EVPI) will be reported, which is defined as the maximum investment a decision-maker would be willing to pay to eliminate all parameter uncertainty from the decision problem. In addition, the expected value of partial perfect information (EVPPI) which evaluates the maximum value of removing all uncertainty in one, or a subset of parameters will be calculated for those parameters which are shown to strongly influence the conclusions. Furthermore, the expected value of sample information (EVSI) which explicitly takes into account that some uncertainty will remain even with large sample sizes would be calculated. EVPI provides an indication of whether a trial, or further research, with an objective of providing more accurate information on one or more variables, would be estimated to be a cost-effective use of resources, and if so, what sample size is estimated to be most cost-effective.

Formal value of information analyses will be undertaken using three approaches of increasing complexity: the expected value of perfect information (EVPI); the expected value of partial perfect information (EVPPI); and the expected value of sample information (EVSI).

EVPI is relatively simple and is a by-product of probabilistic sensitivity analyses. This value is defined as the maximum investment a decision-maker would be willing to pay to eliminate all parameter uncertainty from the decision problem [37] but has the limitation that it assumes all information can be determined with certainty. EVPPI is similar to EVPI, but instead of evaluating the uncertainty associated with all parameters focuses on the uncertainty associated with a subset of one or more parameters, allowing the decision makers to be able to conclude in which variables further research would be most beneficial [38]. The computational time required for EVPPI is markedly more than for EVPI as the process essentially requires two iterations of probabilistic analyses, as standard probabilistic sensitivity analyses are undertaken for each sampled parameter value for the variable(s) under analysis. EVSI addresses the limitation that values for the parameters can be ascertained without uncertainty, which effectively assumes an infinite trial size, and seeks to provide an optimal number of patients to study within a future trial [39]. This value can be zero if it is predicted that the costs of the trial outweigh the benefits accrued. In addition, EVSI also allows the evaluation of marginal returns associated with increased sample size formally taking into account that an additional 100 patients when only 500 have been recruited would be likely to provide more value than when 20,000 have been recruited. Within EVSI the costs of the trial are compared with the benefits achieved in order to find the maximum expected net benefit of sampling, which would correspond with the recommended trial size. In this project, a selection of possible future trials deemed appropriate by the clinical advisors would be evaluated. EVSI, similarly to EVPPI requires two iterations of probabilistic analyses, and additionally the updating of prior information with the simulated results of the future trial to form a posterior distribution. The study team has had experience of performing EVSI on real world problems [40,41].

Project timetable and milestones:

The project will commence on 1st October 2012 and complete by 30th September 2013.

There will be three phases, although development of the model will begin during phase 1:

1. October 2012 to March 2013: Systematic reviews and meta-analysis
2. April to July 2013: Decision analysis modelling
3. August to September 2011: Writing up and dissemination

We will provide one progress report by 31st March 2013 that will report progress with the systematic reviews and meta-analysis.

Expertise:

Steve Goodacre is a leading expert in emergency care research and is Principal Investigator for several major national evaluations. One of his main research interests is using decision analysis modelling and cost-effectiveness analysis to guide policy and practice in emergency care. He has previously led three successfully completed HTA-funded evidence synthesis projects evaluating diagnostic tests for deep vein thrombosis, management of minor head injury and management of suspected acute coronary syndrome.

Matt Stevenson has a wide experience of different mathematical modelling techniques and has worked extensively for NICE and the NCCHTA. He is technical director of SchARR-TAG (one of ten academic units contracted to work for NICE and the HTA) and a member of NICE appraisal committee C. In 2007 he was an invited expert to a NICE workshop to help formulate further the NICE reference case for evaluating the cost-effectiveness of diagnostic techniques, and is a member of the working party currently updating NICE's method guide.

Simon Dixon is a senior health economist who undertook economic analysis for the 3CPO and ESCAPE trials.

John Stevens is Deputy Director of the Centre for Bayesian Statistics in Health Economics (CHEBS) and an expert in the application of Bayesian statistics to economic analysis. He has worked on a variety of projects for NICE and the NCCHTA, and is a member of NICE appraisal committee C. He also has extensive experience of pharmaceutical drug development.

Abdullah Pandor is an experienced systematic reviewer who was project manager for a successful previous HTA-funded evidence synthesis project (07/37/08): The cost-effectiveness of investigation and hospital admission for minor (GCS 13-15) head injury.

Gavin Perkins is a consultant intensivist and co-director of research for the Intensive Care Society (UK). He is the clinical CI on the pre-hospital PARAMEDIC trial of a mechanical CPR device.

Service Users:

The Sheffield Emergency Care Forum (SECF) is a patient and public representative group that provides advice and assistance to researchers in emergency care, reviews research proposals and outputs, facilitates patient and public involvement in emergency care research and organises public meetings to disseminate research findings.

Enid Hirst is Chair of the SECF and has assisted in the development of this proposal. She has previously provided and facilitated patient representation for evaluations led by SG. She established a Cardiac User Group for our recent evaluation of the National Infarct Angioplasty Project (NIAP). This group helped to develop the research plans, guided the development of patient and carer interview schedules, and reviewed the outputs of the project.

The opportunities for user involvement in this project are inevitably limited by the reliance upon secondary data sources. However, we plan to ask Enid and members of the SECF to review the outputs from the project. We will present our findings to SECF in order to identify ways of communicating our findings to the public and explore the public understanding of our findings.

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