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An evaluation of the clinical and cost-effectiveness of pulmonary artery catheters in patient management in intensive care: a systematic review and a randomised controlled trial

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Abstract

An evaluation of the clinical and cost-effectiveness of pulmonary artery catheters in patient management in intensive care: a systematic review and a randomised controlled trial

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Objectives: To evaluate the clinical and cost-effectiveness of managing critically ill patients in adult, general intensive care with or without pulmonary artery catheters (PACs).
Design: An open, multi-centre, randomised controlled trial with economic evaluation (cost–utility and cost-effectiveness analysis).
Setting: The setting was general (mixed medical/surgical) intensive care units (ICUs) in the UK admitting adults.
Participants: Adult patients in participating ICUs deemed by the responsible treating clinician to require management with a PAC.
Interventions: These were insertion of a PAC and subsequent clinical management, at the discretion of the responsible treating clinicians, using data derived from the PAC. The control group were managed without a PAC but with the option of using alternative cardiac output monitoring devices.
Main outcome measures: The main outcome measure was hospital mortality. Secondary outcome measures were length of stay in the ICU, length of stay in an acute hospital and organ-days of support in the ICU. For the economic evaluation, the main outcome measure was quality-adjusted life-years (QALYs) and the secondary outcome measure was hospital mortality.
Results: Sixty-five ICUs in the UK participated. Of these, 43 (66%) used alternative cardiac output monitoring devices in control group patients. A total of 1263 patients were identified as being eligible for the trial. Of these, 1041 (82.4%) were randomised and allocated to management with (n = 519) or without (n = 522) a PAC. There were no losses to follow-up. However, 27 patients (13 in the PAC group and 14 in the control group) were withdrawn from the trial because either the patient withdrew consent on recovering mental competency or the relatives withdrew agreement following randomisation. Data on 1014 patients were included in the analysis. Participants in the two groups had similar baseline characteristics. There was no difference in hospital mortality for patients managed with (68.4%) or without (65.7%) a PAC. The adjusted hazard ratio (PAC versus no PAC) was 1.09 [95% confidence interval (CI) 0.94 to 1.27]. There was no difference in the median length of stay in ICU, the median length of stay in an acute hospital or mean organ-days of support in ICU between the two groups. The economic evaluation found that the expected cost per QALY gained from the withdrawal of PAC was £2985. The expected cost per life gained from the withdrawal of PAC was £22,038.
Conclusions: Clinical management of critically ill patients with a PAC, as currently practised in the UK, neither improves hospital survival for adult, general intensive care patients nor reduces length of stay in hospital. The lack of demonstrable benefit from a device previously believed to be beneficial could be explained by statistical chance, by misinterpretation of PAC-derived data, by ineffective treatment strategies based on data correctly interpreted using the current paradigm or by subsequent inaction following insertion of the device. It is also possible that detailed data on haemodynamics, however used, cannot modify the disease process sufficiently to influence disease outcome. The economic evaluation, using decision analysis techniques rather than conventional hypothesis

testing, suggests that the withdrawal of the PAC from routine clinical practice in the NHS would be considered cost-effective in the current decision-making climate, and might result in lives or life-years being saved at modest cost. With the declining use of PACs in the UK and the findings of this report indicating no overall benefit from management with a PAC, it should now be possible to examine protocolised management with a PAC in selected groups of critically ill patients against appropriate controls, something that was difficult while PACs were the considered standard of care.

Contents

List of abbreviations

ACP	Augmented Care Period
APACHE II	Acute Physiology And Chronic Health Evaluation version II
APS	acute physiology score
ASA	American Society of Anesthesiologists
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CMP	Case Mix Programme
CPAP	continuous positive airway pressure
CUA	cost–utility analysis
CVP	central venous pressure
HDU	high-dependency unit
ICNARC	Intensive Care National Audit and Research Centre
ICU	intensive care unit
IQR	inter-quartile range
LOS	length of stay
LREC	Local Research Ethics Committee
MREC	Multi-centre Research Ethics Committee
NICE	National Institute for Health and Clinical Excellence
OR	odds ratio
PAC	pulmonary artery catheter
PACU	post-anaesthesia care unit
QALY	quality-adjusted life-year
RCT	randomised controlled trial
SCCM	Society of Critical Care Medicine
SD	standard deviation
SEM	standard error of mean
SOFA	Sepsis-related Organ Failure Assessment

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 at the end of the table.

Executive summary

Introduction

Background

Bedside pulmonary artery catheterisation gradually became a standard of care for critically ill patients following its introduction three decades ago. This adoption into mainstream practice occurred without any evaluation of either its clinical or cost-effectiveness. The ongoing, long-standing debate about the clinical effectiveness of pulmonary artery catheters (PACs) was rekindled in 1996 following the publication of a large, non-randomised, risk-adjusted study. The study suggested that patients had an increased odds of dying, within 30 days of admission to an intensive care unit (ICU), if a PAC was used [odds ratio (OR) 1.24, 95% confidence interval (CI) 1.03 to 1.49] and that PACs increased the use of resources. In addition, a contemporaneous, systematic review revealed that that there was very little evidence from randomised controlled trials (RCTs) to support the clinical management of critically ill patients with PACs. We undertook and updated the systematic review to consider the need for an RCT.

Summary of systematic review

Objective

The objective was to search systematically for, and combine, all the evidence from RCTs relating to the effect of the clinical management of critically ill patients with a PAC both on mortality and on the costs of care.

Inclusion criteria

All RCTs, with or without blinding, were included where adult patients were randomised to be managed with or without (control) a PAC, the PAC was inserted in an ICU or during a surgical procedure leading to ICU admission, and either mortality, length of stay in ICU or hospital or the costs of care had been measured. There was no restriction on language. Studies were excluded if a PAC was placed solely for organ support prior to organ donation in patients declared brain dead following brain-stem death testing.

Outcome measures

The primary outcome measure was hospital mortality and the secondary outcome measures were length of stay in ICU and hospital and the costs of care.

Search strategy

The following electronic databases were searched (initially to June 2001, then updated to November 2003): Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE and CINAHL. Conference abstracts from the four major European and North American annual critical care conferences were hand-searched from 1995 to 2001. Reference lists of previous reviews, and both relevant and potentially relevant studies identified from the searches, were checked. Both experts in critical care and manufacturers of PACs were contacted for relevant literature.

Identification of studies

Citations were checked, with respect to the inclusion criteria, by four reviewers working in pairs and the final included studies were agreed by consensus between all reviewers.

Assessment of methodological quality

Included studies were assessed for possible sources of bias as recommended by the UK Cochrane Centre – no 'quality' scale was used.

Analysis

Separate meta-analyses were undertaken, combining data from studies that had included patient populations with similar characteristics. A weighted OR was calculated across studies using a random-effects model (Cochrane statistical package RevMan version 4.2.7). All analyses were based on the results reported on the intention-to-treat principle.

Results

From all searches (to November 2003), 3282 discrete citations were identified. Of these, full paper copies were obtained and reviewed for 39 and, of these, 11 studies were eligible for inclusion. These fell broadly into two groups: studies of general intensive care patients ($n = 3$); and studies of high-risk surgery patients ($n = 8$). The latter group could be further subdivided into those that did ($n = 5$) or did not ($n = 3$) include preoperative optimisation as part of the intervention. Only two

studies were multi-centre (both identified from the updated search). All remaining studies were small, under-powered and in one or two centres. Potential problems of bias existed for four studies, either because the randomisation and concealment methods were inadequate or because there was a high crossover rate from the control to the intervention group. Mortality statistics varied across studies but none reported a statistically significant difference between those managed with or without a PAC. Data pooled for the studies of general intensive care patients (n = 3) yielded an OR of 0.97 (95% CI 0.74 to 1.26) on comparing PAC with no PAC. In the studies of high-risk surgery patients, for studies that did not include preoperative optimisation (n = 3) the pooled OR was 1.10 (95% CI 0.13 to 9.06) and for those that did 0.98 (95% CI 0.72 to 1.33). No studies reported differences in ICU or hospital length of stay. Four studies, conducted in the USA and using hospital charges as a measure of costs of care, indicated that costs were generally higher for patients managed with a PAC, but these results were not statistically significant.

Conclusion

Evidence from RCTs to support the clinical management of critically ill patients with PACs is scant. Initial searching of the literature (to June 2001) identified only one small RCT of general intensive care patients. This study was discontinued prematurely. The remaining seven studies were of high-risk surgery patients. Hence the initial review indicated a clear need for a large multi-centre RCT. Updated searching after the RCT had commenced revealed no conclusive evidence.

Objectives

The objectives were to evaluate the clinical and cost-effectiveness of managing critically ill patients in adult, general intensive care with or without PACs.

Design

The study was an open, multi-centre, RCT with economic evaluation (cost–utility and cost-effectiveness analysis).

Setting

The setting was general (mixed medical/surgical) ICUs in the UK admitting adults.

Participants

The participants in the trial were all adult patients in participating ICUs deemed by the responsible treating clinician to require management with a PAC unless: less than 16 years of age; admitted to ICU electively for preoperative optimisation prior to surgery; a PAC already in place on admission to ICU; had previously been entered into the RCT; or dead using brain-stem death criteria and a PAC being placed for organ support prior to donation.

Interventions

These were insertion of a PAC and subsequent clinical management, at the discretion of the responsible treating clinicians, using data derived from the PAC. The control group were managed without a PAC but with the option of using alternative cardiac output monitoring devices.

Outcome measures

The main outcome measure was hospital mortality. Secondary outcome measures were length of stay in the ICU, length of stay in an acute hospital and organ-days of support in the ICU. For the economic evaluation, the main outcome measure was quality-adjusted life-years (QALYs) and the secondary outcome measure was hospital mortality.

Results

Sixty-five ICUs in the UK participated. Of these, 43 (66%) used alternative cardiac output monitoring devices in control group patients. A total of 1263 patients were identified as being eligible for the trial. Of these, 1041 (82.4%) were randomised and allocated to management with (n = 519) or without (n = 522) a PAC. There were no losses to follow-up. However, 27 patients (13 in the PAC group and 14 in the control group) were withdrawn from the trial because either the patient withdrew consent on recovering mental competency or the relatives withdrew agreement following randomisation. Data on 1014 patients were included in the analysis. Participants in the two groups had similar baseline characteristics. There was no difference in hospital mortality for patients managed with (68.4%) or without (65.7%) a PAC. The adjusted hazard ratio (PAC versus no PAC) was 1.09 (95% CI 0.94 to 1.27). There was

no difference in the median length of stay in ICU, the median length of stay in an acute hospital or mean organ-days of support in ICU between the two groups. The economic evaluation found that the expected cost per QALY gained from the withdrawal of PAC was £2985. The expected cost per life gained from the withdrawal of PAC was £22,038.

Conclusions

Clinical management of critically ill patients with a PAC, as currently practised in the UK, neither improves hospital survival for adult, general intensive care patients nor reduces length of stay in hospital. The lack of demonstrable benefit from a device previously believed to be beneficial could be explained by statistical chance, by misinterpretation of PAC-derived data, by ineffective treatment strategies based on data correctly interpreted using the current paradigm or by subsequent inaction following insertion of the device. It is also possible that detailed data on haemodynamics, however used, cannot modify the disease process sufficiently to influence outcome. The economic evaluation, using decision analysis techniques rather than conventional hypothesis testing, suggests that the withdrawal of the PAC from routine clinical practice in the NHS would be considered cost-effective in the current decision-making climate, and might result in lives or life-years being saved at modest cost.

Future research

The use of PACs is declining in the UK, predominately because other, less invasive technologies for measuring cardiac output are now becoming available. As it is unclear whether deriving detailed haemodynamic data, from a PAC or from any other means, affects outcome in critically ill patients, these new devices must be subjected to proper evaluation. Ideally, it needs to be determined whether the lack of effectiveness seen in this study is unique to PACs or is a 'class effect' of all haemodynamic monitors measuring cardiac output. This study examined the effectiveness of clinical management of critically ill patients with a PAC (a package of pulmonary artery catheterisation and subsequent unprotocolised management) in a heterogeneous population of critically ill patients. By indicating no overall benefit from management with a PAC, it should now be possible to examine protocolised management with a PAC in selected groups of critically ill patients against appropriate controls, something that was difficult while PACs were the considered standard of care.

Chapter 1
Introduction

Pulmonary artery catheterisation was first introduced into medicine in 1944[1] and was used initially to assess the severity of mitral valve disease. The pulmonary artery catheter (PAC) was inserted into the venous circulation, usually via one of the large veins in the groin, arm, neck or chest, and advanced through the chambers of the right side of the heart and into the pulmonary artery. It was then advanced until its tip temporarily occluded the branch of the pulmonary artery in which it sat. This interruption of forward flow allowed pressure measured at the catheter tip to reflect filling pressures in the left side of the heart, at the end of the occluded pulmonary vessel. The degree of elevation of this pressure was a measure of the severity of mitral valve disease. The procedure was largely confined to cardiac catheterisation laboratories. The introduction of the balloon flotation catheter in the 1970s allowed insertion of these catheters at the bedside without the need for X-ray guidance to position the catheter correctly in the pulmonary artery.[2] This changed what was primarily a one-off diagnostic procedure into a monitoring technique with continuous or intermittent measurement and display of pressures in the right atrium, right ventricle, pulmonary artery and left atrium. Nearly all types of PAC are also capable of measuring blood flow through the heart, that is, the cardiac output.

The technique gradually became accepted as the gold standard method to measure cardiac output and other haemodynamic variables. The concept that detailed knowledge of haemodynamic variables in critically ill patients would translate to a survival advantage was widespread, and so the PAC became a standard of care without evaluation of either its clinical or cost-effectiveness. PACs are now usually used to monitor patients with severe cardiac or respiratory failure. They are used to guide treatment with fluids and inotropic (cardiac stimulant) drugs during the most severe phase of the illness. Most are fitted with devices to measure cardiac output and are often connected to monitors that display not only the primary variables (pressures and cardiac output) but also secondary derived measures of adequacy of the circulation such as resistance to blood flow. They are introduced into the circulation, generally via one of the large veins in the neck or chest, and usually stay in place for a few days. The PAC and other devices available to measure cardiac output are described in detail in Appendix 1.

With the possible exception of electronic foetal monitoring, no monitoring device has polarised opinion as much as the PAC.[3–7] Proponents argue for its unique ability to allow accurate measurement of cardiac output and other haemodynamic variables, allowing improved diagnosis and management of circulatory instability.[6,7] Critics point to complications associated with its insertion and use,[3–5,8,9] inaccuracies in measurement, poor interpretation of data[10–12] and the lack of positive outcome benefits with suggestions of increased mortality from retrospective analyses.[13,14]

In 1996, a comprehensive review of all available comparative and randomised clinical trials involving pulmonary artery catheterisation was published.[15] Of 34 published studies reviewed, only one was considered 'level 1' evidence.[16] This showed no benefit for treatment aimed at achieving 'goal' values for haemodynamic variables (goal-directed therapy) in a mixed intensive care population. The remaining studies were equally split between those showing no difference or worsened outcome with the PAC and those showing a benefit. Thus there was no clear indication that the PAC improves outcome. Furthermore, many of these studies involving the PAC were trials of preoperative optimisation, which involves an overall package of enhanced care on an intensive care unit (ICU), of which the PAC is only one component, or trials of goal-directed therapy where outcome may be primarily determined by other components of the algorithm, such as blood transfusion. Pragmatic studies of PAC use following admission to the ICU, the commonest clinical situation, were virtually non-existent; only one randomised controlled trial (RCT) was identified, which was discontinued prematurely because of poor recruitment and which had a cross-over rate from the control to treatment group of nearly 50%.[17] In this trial, of 148 eligible patients in two participating hospitals, only 33 (22.3%) were recruited. Of the 17 patients allocated to the

control group (not to be managed with a PAC), eight had a PAC inserted following randomisation. Ethical concerns were the most frequently cited reason for not recruiting eligible patients.

This long-standing debate about the clinical effectiveness of PACs was rekindled with the publication of a large, non-randomised, risk-adjusted study by Connors and colleagues in 1996,[18] which suggested an increased odds of 30-day mortality [odds ratio (OR) 1.24, 95% confidence interval (CI) 1.03 to 1.49] in patients managed with a PAC during the first 24 hours following admission to ICU, and increased utilisation of resources. The media coverage in the USA[19–21] that followed publication of the study led to a formal press release from the Society of Critical Care Medicine (SCCM)[22] challenging the conclusions of the study, predominantly because it was a non-randomised comparison. In December 1996, the SCCM convened a multidisciplinary Consensus Conference on the PAC. A Consensus Statement was published in June 1997.[7] In general, the statement identified that the level of published evidence to support the use of PAC was paltry and, scientifically, very poor. However, the statement supported the continuing use of PACs.

Although widely discussed, the Consensus Statement did not help clarify the indications for a PAC. It was, in scientific terms, an unsystematic, narrative review.[23] The potential for biased selection of the conference participants was not addressed and, unlike the review cited above, the selection and review of the evidence were not based on any defined criteria. The Consensus Statement relied on 'expert opinion' for response and the method of consensus for that response was, therefore, of paramount importance. Explicit scientific methods exist for reaching consensus, for example, nominal group or Delphi techniques,[24] but none were used.

The Connors and colleagues' study also provoked numerous editorials in scientific journals concerning the clinical and cost-effectiveness of the PAC.[5,25,26] In the UK, the correspondence that followed[27–29] the editorial published in the *BMJ*[26] suggested there was considerable equipoise amongst UK clinicians. In 1997, MacKirdy and colleagues[30] conducted a similar risk adjusted comparison of patients managed with and without a PAC using Scottish data, and reported similar results to Connors and colleagues.

This led the Intensive Care National Audit and Research Centre (ICNARC) to respond to the 'Consultation to identify National Health Service Research and Development Priorities' in October 1996 by identifying the PAC as a technology urgently requiring evaluation.

The proposed study needed not only to address the clinical and cost-effectiveness of the PAC as currently used in the NHS but also to address the criticisms levelled at previous studies. Therefore, the study consisted of three distinct activities:

1. a systematic review of the evidence on the PAC to inform the final design of the subsequent RCT
2. a multi-centre, open, RCT to evaluate the clinical effectiveness of PACs in patient management in adult, general intensive care
3. an economic evaluation of the cost-effectiveness of PACs in patient management in adult, general intensive care.

Chapter 2

Systematic review

Objective

The objective was to search systematically for and combine all the evidence from RCTs evaluating the effect of management of intensive care patients with PACs on mortality and the costs of care.

Criteria for considering studies

All RCTs, with or without blinding, in which patients were allocated to be managed with a PAC (of any type) in one arm or to be managed without a PAC in another (control) arm were considered. Additional criteria for the selection of studies were that:

- More than 50% of the participants in the trial were adult (16 years of age and above).
- The PAC was placed in a critical care unit or was placed during a surgical procedure leading to admission to a critical care unit [a critical care unit was defined as either an ICU, a high-dependency unit (HDU), a post-anaesthesia care unit (PACU) or a service specific critical care unit].
- One or more of the following outcomes had been measured: mortality (ICU, 28-day, 30-day, hospital); length of stay in ICU; length of stay in hospital; or costs of care.

Studies were excluded if there were participants who had been declared brain dead using brain stem death criteria, where a PAC was being placed solely for organ support prior to donation.

Primary and secondary outcome measures

The primary outcome measure was hospital mortality. The secondary outcome measures were length of stay in ICU, length of stay in hospital and costs of care.

Methods

Search strategy

Previous reviews

We reviewed the studies cited in a previously published review.[15]

Electronic searches

We searched the Cochrane Central register of Controlled Trials (CENTRAL) in the Cochrane Library, issue 4, 2001, MEDLINE (all records to June 2001), EMBASE (all records to June 2001), CINAHL (all records to June 2001) and SIGLE (all records to June 2001). The search strategy used the optimum terms recommended by the Cochrane Collaboration to identify RCTs combined with terms to identify studies involving PACs (Appendix 2) and was adapted according to the database searched. There was no restriction on the language of published studies. At the end of 2003, the search described above was updated to include all records to November 2003.

Manual searches

Conference abstracts from the four major European and North American annual critical care conferences, run by the European Society of Intensive Care Medicine, the SCCM, the American Thoracic Society and the Erasme Hospital, Free University of Brussels, were searched from 1995 to 2001.

Snowballing

The reference lists of potentially relevant citations, identified from the electronic searches, and the included studies were checked for further relevant studies. The reference lists of any systematic or narrative reviews identified from the searches were also checked.

Experts

Key people in the field of critical care were contacted, including clinicians and other researchers. The final list of identified studies was circulated to delegates at a PAC-Man Study Collaborators' Meeting with a request for information on any missed studies.

Industry

Manufacturers of the PAC were contacted.

Identification of studies

The citations generated from the database searches were divided between two pairs of reviewers, working independently. The titles and abstracts of the citations were screened for potentially relevant studies. The full texts of all potentially relevant

citations were obtained, divided between the two pairs of reviewers and assessed independently by each reviewer for inclusion. The final selection of studies for inclusion was made by consensus between the four reviewers.

Data extraction

The full-text paper of each included study was reviewed by two reviewers independently and the following data were extracted using the data collection form (Appendix 3):

- general information, including title, lead author, journal, publication details and name of reviewer
- study characteristics, including verification of study eligibility, characteristics of the study population, methodological quality of the study, interventions and outcomes
- outcome measures and results, including length of follow-up, drop-outs and measures of effect.

Data were double-checked and entered into RevMan 4.2.7, a software program distributed by the Cochrane Collaboration to record the results of systematic reviews and perform meta-analyses.

Assessment of methodological quality

Methodological quality of the trials was assessed as recommended by the UK Cochrane Centre.[31] Possible sources of bias, selection bias, performance bias, attrition bias and detection bias were described. Scales for measuring the validity or 'quality' of trials exist, but were not used for the current review.

Data synthesis

The aims, methods and outcome measures of interest (mortality, length of stay in ICU and hospital and costs of care) were summarised for each included study. Mortality was expressed as absolute numbers and percentages and lengths of stay were expressed as mean, median and range, for survivors and non-survivors separately, where reported. Results on costs of care were expressed in a range of measures.

Patients admitted to ICU are a heterogeneous group in terms of diagnosis, prognosis and resource utilisation. This heterogeneity exists both between patients within a single ICU and between the case mix of patients admitted to individual ICUs, and it would be inappropriate to combine data from studies of different patient populations into one meta-analysis. Therefore, separate meta-analyses were undertaken combining data from studies that had included patient populations with similar characteristics. Studies that had included other interventions in addition to the PAC were also combined in a separate meta-analysis. For studies that had two PAC intervention groups, the two groups were combined. The outcome measure of interest was hospital mortality; however, if this was not reported, the mortality at the point closest to hospital discharge was used. A weighted OR was calculated across studies using a random effects model in the Cochrane statistical package RevMan version 4.2.7. All analyses were based on the intention-to-treat principle.

Results

A total of 3282 discrete citations were identified from the database searches, manual searches, snowballing and contact with experts. After screening by title and then abstract, full paper copies were obtained for 39 citations. Of these, 11 studies were identified from both the original and updated searches[17,32–41] (*Figure 1*). The 28 citations[42–69] that were excluded following full paper review are listed in *Table 1* with the reasons for exclusion.

Description of included studies

The 11 studies that met the inclusion criteria[17,32–41] and were included in the review fell broadly into two groups as follows:

1. First were studies of general intensive care patients, where patients were randomised to management with a PAC, or management without, following admission to the ICU. Three studies (*Table 2*) were identified. One was a two-centre trial in Canada,[17] one was a single-centre trial in the UK[32] and one was a multi-centre trial (36 hospitals) in France.[33]
2. Second were studies of high-risk surgery patients, which can be further subdivided into those that did not include preoperative optimisation as part of the intervention[34–36] and those that did.[37–41] Eight studies were identified (*Table 2*). Seven were single-centre trials in the USA,[34–40] and one was a multi-centre trial (19 hospitals) in Canada.[41]

Methodological quality of studies

Selection bias

Five of the studies[17,32,33,39,41] clearly used adequate randomisation and concealment schemes (*Table 2*). One study[34] did not use adequate concealment, although the two groups of patients were fairly well balanced at baseline for numbers of patients, age and American Society of Anesthesiologists

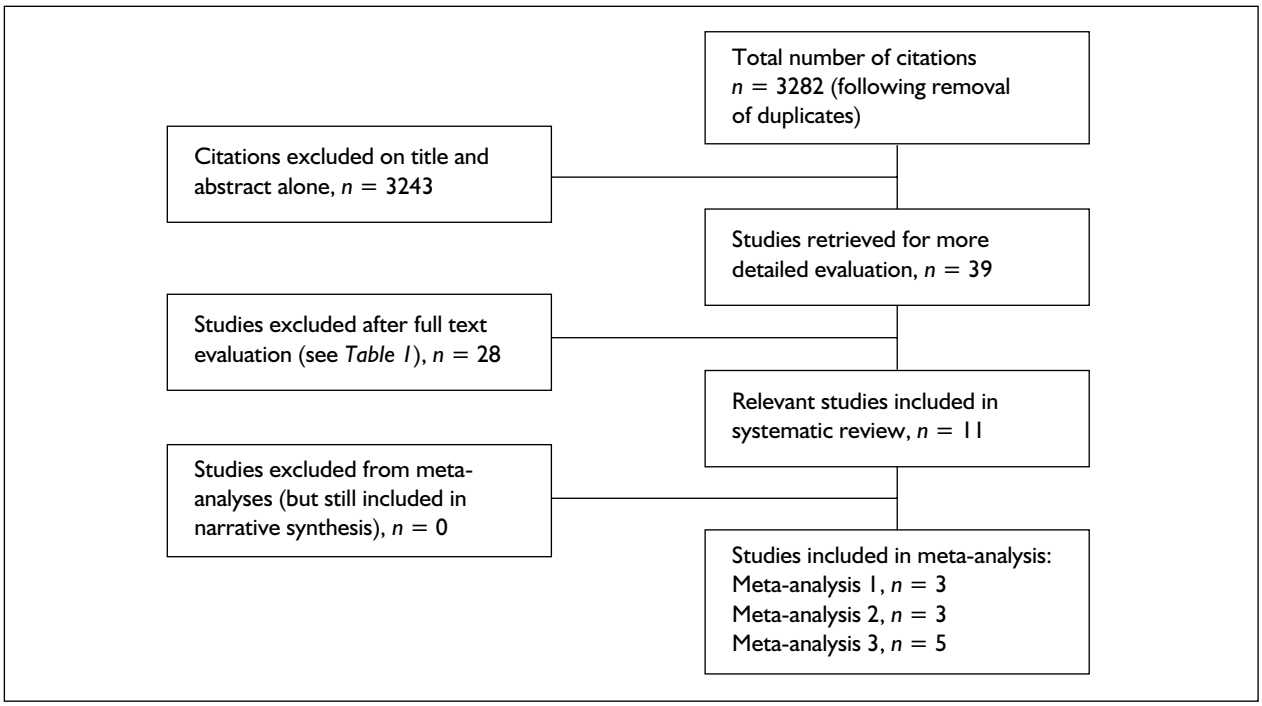


FIGURE 1 *Flow diagram of study selection process*

TABLE 1 *Studies excluded following full paper review*

Study	Reason for exclusion
Schultz *et al.*, 1985[42]	Not all patients assigned to the control group were transferred to ICU or HDU following surgery
Orlando *et al.*,1985[43]	Conference abstract only
Senagore *et al.*, 1987[44]	Not an RCT comparing management with and without a PAC
Raybin, 1989[45]	Letter
Tuman *et al.*, 1989[46]	Not an RCT
Eyer *et al.*, 1990[47]	Not an RCT comparing management with and without a PAC
Shoemaker *et al.*, 1990[48]	Patients were randomly allocated in the second part of the study only. In addition, there were no clear data on mortality in the two groups
Mermel *et al.*, 1991[49]	Not an RCT
Cobb *et al.*, 1992[50]	Not an RCT comparing management with and without a PAC
Mitchell *et al.*, 1992[51]	Not an RCT comparing management with and without a PAC
Bach *et al.*, 1992[52]	Not an RCT comparing management with and without a PAC
Bach *et al.*, 1992[53]	Not an RCT comparing management with and without a PAC
Sola and Bender, 1993[54]	Review article
Yu *et al.*, 1993[55]	Not an RCT comparing management with and without a PAC
Kearns, 1993[56]	Summary of a previously reported RCT[50]
Boyd *et al.*, 1993[57]	Not an RCT comparing management with and without a PAC
Yu *et al.*, 1995[58]	Not an RCT comparing management with and without a PAC
Boldt *et al.*, 1995[59]	Not an RCT comparing management with and without a PAC
Brazzi *et al.*, 1995[60]	Not an RCT comparing management with and without a PAC
Holmes *et al.*, 1997[61]	Not an RCT
Ziegler *et al.*, 1997[62]	Not an RCT comparing management with and without a PAC
Latour-Perez and Calvo-Embuena, 1998[63]	Not an RCT
Cohen *et al.*, 1998[64]	Not an RCT comparing management with and without a PAC
Stewart *et al.*, 1998[65]	Not an RCT
Girbes *et al.*, 1999[66]	Study end-point was the commencement of surgery
Wilson *et al.*, 1999[67]	Not all patients assigned to the control group were transferred to ICU or HDU following surgery
Barone *et al.*, 2001[68]	Review and meta-analysis
Bonazzi *et al.*, 2002[69]	Patients assigned to the control group were not transferred to ICU or HDU following surgery

TABLE 2 *Description of included RCTs*

Study	Main aim	Selection criteria	Outcomes	*A priori* sample size calculation?	Total eligible, *n*	Total randomised, *n*	Randomisation/allocation procedure
Studies of general ICU patients: management with a PAC versus management without a PAC							
Guyatt, 1991[17]	To investigate the impact of right heart catheterisation on physiological status and stay in the ICU	**Entry criteria:** Assisted ventilation; hypotension with CVP $\geq$10 cm H_2O; oliguria with CVP $\geq$10 cm H_2O; oliguria with hypoxaemia; hypoxaemia and CVP $<$10 cm H_2O; physician believed patient might benefit from a PAC **Exclusion criteria:** PAC ethically contraindicated; PAC an ethical imperative; PAC placed pre-operatively for intraoperative monitoring; organ transplant surgery; receiving high frequency jet ventilation; consent from a close relative not obtained	Mortality (not defined), ICU LOS Main outcome not stated	No	148	33	Computer-generated random numbers stored in sequentially marked envelopes, which were checked daily
Rhodes *et al.*, 2002[32]	To compare survival and clinical outcomes of critically ill patients managed with a PAC compared with those managed without	**Entry criteria:** Circulatory shock-heart rate $>$100 beats/min, systolic BP $<$100 mmHg, unresponsive to 500 ml fluid challenge; oliguria-urine output $<$0.5 ml/kg/h despite 500 ml fluid challenge; requirement for vasoactive infusion; need for mechanical ventilation **Exclusion criteria:** less than 18 years of age; admitted to ICU for preoperative optimisation	**Primary** 28-day mortality and morbidity Also reported: ICU LOS Hospital LOS	No[a]	202	202 (1 patient withdrawn following randomisation)	Computer-generated random numbers stored in sealed envelopes

continued

TABLE 2 *Description of included RCTs (cont'd)*

Study	Main aim	Selection criteria	Outcomes	*A priori* sample size calculation?	Total eligible, *n*	Total randomised, *n*	Randomisation/allocation procedure
Richard *et al.*, 2003[33]	To compare 28-day mortality in patients managed with and without a PAC	**Entry criteria:** Circulatory shock (according to defined criteria); acute respiratory failure >24 hours **Exclusion criteria:** Less than 18 years old; cardiogenic shock; platelets <10,000; patient not committed to full treatment; moribund; enrolled in another RCT	**Primary** 28-day mortality **Secondary** 14-day mortality 90-day mortality ICU LOS Hospital LOS Morbidity (defined)	90% power to detect 10% difference in mortality. *n* = 1000	Not reported	681 (5 patients withdrawn following randomisation)	24-hour central telephone randomisation service
Studies of high-risk surgery patients: management with a PAC versus management without a PAC							
Isaacson *et al.*, 1990[34]	To determine whether monitoring with PAC or a CVP catheter results in a difference in patient outcome	**Entry criteria:** Elective abdominal aortic reconstructive surgery **Exclusion criteria:** Severe, inoperable coronary artery disease; cor pulmonale; uncompensated congestive heart failure; documented cardiomyopathy; poor left ventricular function (ejection fraction <40%); symptomatic valvular disease; renal failure (blood urea nitrogen >60); severe restrictive/obstructive pulmonary disease (vital capacity <50% of predicted volume); declined consent; emergency aortic procedures	Intraoperative and postoperative fluid requirements Perioperative morbidity (defined) Events related to either the CVP catheter or PAC ICU LOS Hospital LOS Costs of care Also reported: Hospital mortality Main outcome not stated	No	151	102	Top card taken from marked, shuffled cards placed face down in a file

continued

TABLE 2 *Description of included RCTs (cont'd)*

Study	Main aim	Selection criteria	Outcomes	*A priori* sample size calculation?	Total eligible, *n*	Total randomised, *n*	Randomisation/allocation procedure
Joyce *et al.*, 1990[35]	To test the hypothesis that central haemodynamic monitoring is not necessary in potentially 'low-risk' patients undergoing abdominal aortic surgery	**Entry criteria:** Elective infra-renal aortic reconstructive surgery **Exclusion criteria:** Unstable angina; recent myocardial infarction (≤6 months); left ventricular ejection fraction (LVEF) <50%	Perioperative haemodynamics, fluid and cardiac drug administration, operation time and clamp time Postoperative renal function Postoperative ventilation Line complications ICU LOS Hospital LOS 30-day post-operative mortality Main outcome not stated	No	Not clear	40	'Sealed envelope technique'. No other details given
Pearson *et al.*, 1989[36]	To determine if the use of PAC compared with a CVP catheter is associated with decreased morbidity, mortality or costs	**Entry criteria:** Scheduled for elective cardiac surgery **Exclusion criteria:** None reported	ICU mortality morbidity (not defined), costs of care Also reported: ICU LOS Main outcome not stated	No	Not clear	226	Table of random numbers. No other details given

continued

TABLE 2 *Description of included RCTs*

Study	Main aim	Selection criteria	Outcomes	*A priori* sample size calculation?	Total eligible, *n*	Total randomised, *n*	Randomisation/allocation procedure
Studies of high-risk surgery patients: management with a PAC + preoperative optimisation versus management without a PAC + usual preoperative care							
Bender *et al.*, 1997[37]	To determine whether placement of a PAC with optimisation of haemodynamics results in outcome improvement after elective vascular surgery	**Entry criteria:** Scheduled for elective infrarenal aortic reconstruction or lower limb revascularisation (by one surgeon) **Exclusion criteria:** Anticipated need before surgery for suprarenal or supracoeliac clamping; myocardial infarction within 3 months or inadequately controlled angina; poorly compensated congestive heart failure; coronary artery bypass surgery within 6 weeks; symptomatic aortic/mitral valvular disease	Adverse outcomes (defined) including 30-day mortality Main outcome not stated	No[b]	104	104	Not described
Berlauk *et al.*, 1991[38]	To test the hypothesis that optimising haemodynamics using a PAC would improve outcome in patients undergoing limb-salvage arterial surgery	**Entry criteria:** Scheduled to receive an *in situ* vein graft bypass for lower limb vascular insufficiency **Exclusion criteria:** Myocardial infarction within 3 months; coronary artery bypass graft within 6 weeks; uncompensated congestive heart failure; severe valvular disease; unstable angina	**Primary** Cardiovascular complications, e.g. congestive cardiac failure, arrhthymia, myocardial infarction **Secondary** Immediate postoperative graft thrombosis and adverse intraoperative events Also reported: Mortality (not defined)	No	Not clear	89	Random number generator. Patients entered consecutively in order of appearance on the surgical schedule. No other details given

continued

TABLE 2 *Description of included RCTs (cont'd)*

Study	Main aim	Selection criteria	Outcomes	*A priori* sample size calculation?	Total eligible, *n*	Total randomised, *n*	Randomisation/allocation procedure
Sandham *et al.*, 2003[41]	To compare goal-directed therapy guided by a PAC with standard care without the use of a PAC in high-risk surgical patients	**Entry criteria:** Age ≥60 years; ASA class III or IV risk; scheduled for urgent/elective major abdominal, thoracic, vascular or orthopaedic surgery	**Primary** Hospital mortality **Secondary** 6-month mortality 12-month mortality Hospital morbidity (defined)	90% power to distinguish between hospital mortality rates of 10 and 15% in the two groups	3803	1994	Computer-generated sequence concealed in sealed, opaque, consecutively numbered envelopes. Stratified according to type of surgery, ASA class and blocked according to centre
Shoemaker *et al.*, 1988[39]	To compare outcomes of patients whose therapeutic goals were to maintain normal haemodynamic values with those whose goals were to attain supranormal values empirically observed in critically ill postoperative survivors	**Entry criteria:** Patients with one or more high of 11 high-risk criteria previously defined and associated with a mortality rate close to 30% **Exclusion criteria:** None reported	Mortality and morbidity (not defined) Main outcome not stated	No	146	91	Cards arranged according to random numbers tables, by an outside person, placed in sealed, opaque envelopes, opened in sequence

continued

TABLE 2 *Description of included RCTs (cont'd)*

Study	Main aim	Selection criteria	Outcomes	*A priori* sample size calculation?	Total eligible, *n*	Total randomised, *n*	Randomisation/allocation procedure
Valentine *et al.*, 1998[40]	To determine whether the morbidity and mortality rates of aortic surgery are reduced by preoperative haemodynamic optimisation and perioperative monitoring with a PAC	**Entry criteria:** Elective abdominal aortic reconstruction. **Exclusion criteria:** Myocardial infarction within 3 months; coronary artery bypass surgery within 6 weeks; severe aortic/mitral valve disease; unstable angina/recent change in angina symptoms; clinically overt congestive cardiac failure; advanced chronic renal insufficiency; redo aortic operations; additional procedures, e.g. renal artery bypass grafting performed	Adverse postoperative events (defined) Duration of ventilation ICU LOS Hospital LOS Hospital mortality Main outcome not stated	No	126	120	Sealed envelopes. No other details given

BP, blood pressure; CVP catheter, central venous pressure catheter (see appendix 1 for description); LOS, length of stay.

[a] Authors noted that as there were no prospective data on which to perform a power calculation, the study was designed as a pilot with the intention to recruit 200 patients so that future trials could be appropriately powered.

[b] Authors noted that the study as originally designed was expected to show a significant decrease in complications after 200 patients were enrolled.

(ASA) classification. Two studies[35,40] used sealed envelopes but gave no further details; both studies reported that the patient characteristics at baseline were similar in the two treatment groups, although one[35] did not present data in the paper. In addition, this study also included a non-randomised group of patients (n = 11), although no information was given as to how these patients were selected. All data from the two randomised groups were compared with the non-randomised group in the analysis. One study[38] reported that a random number generator was used and that patients were first randomised into two groups. One group was allocated to PAC group 1 and in the other patients were further randomised into two more groups and allocated to either PAC group 2 or the control group. This meant that the three groups were not balanced; 45 patients were allocated to PAC group 1, 23 to PAC group 2 and 21 to the control group. There were also differences between the groups with regard to past medical history of angina, congestive cardiac failure and hypertension. One study used a randomisation and concealment scheme that was clearly inadequate.[36] In this study, a table of random numbers was used to allocate patients to one of three groups: 'standard' PAC group, 'continuous mixed-venous oxygen monitoring' PAC group or control group. However, the authors reported that 'ethical considerations' (which were not described) led to the reassignment of some patients allocated to the control group (based on the patient's hospital number). Forty-six (62%) control patients were reassigned to be monitored using one or other of the two PACs under study. These patients were analysed as separate groups. Thus there were five study groups with an uneven distribution of patients. The patient characteristics of the five groups at baseline were not reported. There was one study[37] in which the randomisation and allocation procedure was not described and, although the two groups were similar for age and sex, a slightly higher proportion of patients in the PAC group required aortic surgery (53%) or had a past history of hypertension (53%) compared with the control group (38% and 30%, respectively).

Performance bias

The intervention under study – management with a PAC – meant that it was not possible to blind study investigators (or participants) to the assigned treatment group. However, except for one study,[36] there was no indication of systematic differences in the care provided to participants other than the intervention under study. The study by Pearson and colleagues[36] evaluated two types of PAC, one of which allowed continuous monitoring of mixed venous oxygen saturation. The authors reported that prior to commencement of the trial, the ICU nurses and house-staff physicians underwent specific in-service training in mixed venous oxygen saturation monitoring. Staff were not informed that the purpose of the study was a cost–benefit analysis, but were rather encouraged to utilise the information provided by the mixed venous oxygen PAC to reduce the number of cardiac output and laboratory determinations.

Attrition bias

For all studies, the numbers of patients withdrawn following randomisation was low (*Table 3*). However, for two studies,[17,39] there was a high rate of crossover from the control group (*Table 3*). Guyatt[17] reported that of the 17 patients allocated to the control group, eight (47%) were subsequently managed with a PAC and Shoemaker and colleagues[39] reported that 17 (57%) patients allocated to the control group were subsequently managed with a PAC during the postoperative period.

Detection bias

As noted previously, the nature of the intervention under study meant that blinding was not possible. There was no evidence of systematic differences between the treatment groups with regard to outcome assessment, although Valentine and colleagues[40] reported that two patients in the control group developed profound shock soon after induction of anaesthesia and needed to be managed with a PAC. The operations were cancelled and the patients transported to the ICU for observation. Placement of a PAC was considered a study end-point in both cases. These patients were included in the analysis of complications on the basis of intention-to-treat but were not included in the outcome analysis.

Mortality

Overall, only three studies[34,39,41] reported hospital mortality. The remainder either reported 28-day mortality,[32,33] 30-day mortality[35,37] or ICU mortality.[36] There were three studies[17,38,39] that reported mortality but did not specify the type of mortality statistic.

Studies of general ICU patients (n = 3)

Two studies[32,33] reported 28-day mortality (*Table 3*). Neither study detected a statistically significant difference between the two treatment groups. The other study by Guyatt[17] did not specify the mortality time point but reported a higher mortality rate in the PAC group (63%)

TABLE 3 *Main results of included RCTs*

Study	Treatment allocation	Withdrawn after randomisation, *n*	Crossovers	Main results	*p* (95% CI)
Studies of general ICU patients: management with a PAC versus management without a PAC					
Guyatt, 1991[17]	**PAC, *n* = 16:** PAC placed and used at the discretion of the attending physician (no protocol) **Control, *n* = 17:** Usual care but managed without a PAC	0	PAC: 0 Control: 8	**Mortality (not specified)** PAC: 10/16 (63%) Control: 9/17 (53%) **ICU LOS, mean days** (survivors) PAC: 10.3 Control: 8.1	 0.58 (–43.1 to 24.0%) 0.58 (–10.2 to 5.8)
Rhodes *et al.*, 2002[32]	**PAC, *n* = 96:** PAC placed and used at the discretion of attending clinician (no protocol) **Control, *n* = 105:** Usual care without a PAC or any other form of cardiac output monitoring	1	PAC: 0 Control: 1 (withdrawn from study and not included in analyses)	**28-day mortality** PAC: 46/96 (47.9%) Control: 50/105 (47.6%) **ICU LOS, median (IQR) days Survivors:** PAC: 10 (2, 14) Control: 6 (2, 13) **Hospital LOS, median (IQR) days Survivors:** PAC: 29 (15, 54) Control: 25(15, 53)	 >0.99 (–13 to 14%) 0.27 (–2.4 to 7.5) 0.81 (–17 to 18)
Richard *et al.*, 2003[33]	**PAC, *n* = 335:** PAC placed and used at the discretion of attending clinician (no protocol) **Control, *n* = 341** Standard care without a PAC	5	PAC: 6 Control: 15	**28-day mortality** PAC: 199/335 (59.4%) Control: 208/341 (61%)	
Studies of high-risk surgery patients: management with a PAC versus management without a PAC					
Isaacson *et al.*, 1990[34]	**PAC, *n* = 49:** PAC placed **Control, *n* = 53:** CVP catheter placed	0	PAC: 0 Control: 1	**Hospital mortality** PAC: 1/49 (2.0%) Control: 0/53 **ICU LOS, mean (SD) days** PAC: 2.7 (2.6) Control: 2.1 (1.0) **Hospital LOS, mean (SD) days** PAC: 10.2 (8.4) Control: 9.4 (6.8)	 0.13 0.60

continued

TABLE 3 *Main results of included RCTs (cont'd)*

Study	Treatment allocation	Withdrawn after randomisation, *n*	Crossovers	Main results	*p* (95% CI)
Joyce *et al.*, 1990[35]	**PAC, *n* = 21** PAC placed **Control, *n* = 19** CVP catheter placed	0	PAC: 0 Control: 0	30-day post-operative mortality PAC: 0/21 Control: 0/19	
Pearson *et al.*, 1989[36]	**PAC 1, *n* = 86:** Standard PAC placed **PAC 2, *n* = 66:** Fibre-optic infrared mixed venous oxygen monitoring PAC placed **Control, *n* = 74:** CVP catheter placed	0	PAC 1: 0 PAC 2: 0 Control: 46 – re-randomised to standard PAC (*n* = 33) or fibre-optic mixed venous oxygen measuring PAC (*n* = 13) and analysed as separate groups	**ICU mortality** PAC 1: 0/86 PAC 2: 1/66 (1.5%) Control: 1/74 (1.4%) **ICU LOS, mean (SD) days** PAC 1: 1.6 (1.1) PAC 2: 2.1 (4.1) Control: 1.4 (1.1) (excludes 46 crossovers)	
Studies of high-risk surgery patients: management with a PAC + preoperative optimisation versus management without a PAC + usual preoperative care					
Bender *et al.*, 1997[37]	**PAC, *n* = 51** Transfer to ICU, PAC placed followed by 'optimisation' preoperatively using a treatment algorithm **Control, *n* = 53** Standard care without a PAC. Arterial and CVP catheters placed All patients admitted to ICU postoperatively	0	PAC: 0 Control: 1	**30-day mortality:** PAC: 1/51 (2.0%) Control: 1/53 (1.9%) **ICU LOS, mean (SD) days** PAC: 2.7 (0.2) Control: 2.6 (0.5) **Hospital LOS, mean (SD) days** PAC: 12.5 (1.4) Control: 12.0 (1.3)	

continued

TABLE 3 *Main results of included RCTs (cont'd)*

Study	Treatment allocation	Withdrawn after randomisation, *n*	Crossovers	Main results	*p* (95% CI)
Berlauk *et al.*, 1991[38]	**PAC 1, *n* = 45** Transfer to ICU, PAC placed followed by 'tune-up' treatment (using predefined end-points) at least 12 h preoperatively **PAC 2, *n* = 23** Transfer to anaesthetic holding area, PAC placed followed by 'tune-up' treatment (using predefined end points) at least 3 h preoperatively. **Control, *n* = 21** Usual care without a PAC. Arterial and CVP catheters placed All patients admitted to ICU postoperatively	0	PAC 1: 0 PAC 2: 0 Control: 1	**Mortality (not specified)** PAC 1: 1/45 (2.2%) PAC 2: 0/23 Control: 2/21 (9.5%) **ICU LOS, mean (SD) days** PAC 1: 3.5 (2.0) PAC 2: 2.5 (1.3) Control: 2.6 (2.1) **Hospital LOS, mean (SD) days** PAC 1: 19.4 (11.6) PAC 2: 18 (12.0) Control: 15.4 (7.5)	0.08 (PAC 1 and PAC 2 vs control)
Sandham *et al.*, 2003[41]	**PAC, *n* = 997** PAC placed prior to surgery, followed by treatment directed to predefined physiological goals **Control, *n* = 997** Standard care without a PAC. Placement of CVP catheter permitted All patients admitted to ICU postoperatively	0	PAC: 58 Control: 52	**Hospital mortality** PAC: 78/997 (7.8%) Control: 77/997 (7.7%) **Hospital LOS, median (IQR) days** PAC: 10 (7–15) Control: 10 (7–15)	0.93 0.41
Shoemaker *et al.*, 1988[39]	**PAC control, *n* = 30** Transfer to ICU. PAC placed followed by standard management to achieve normal values of haemodynamic and oxygen transport variables **PAC protocol, *n* = 28** Transfer to ICU. PAC placed followed by treatment to achieve supra-normal haemodynamic and oxygen transport values **Control, *n* = 30** CVP catheter placed. Standard care All patients admitted to ICU postoperatively	3	PAC control: 0 PAC protocol: 0 Control: 17	**Postoperative mortality (not specified)** PAC control: 10/30 (33%) PAC protocol: 1/28 (3.6%) Control: 7/30 (23%) **ICU LOS, mean (SD) days** PAC control: 15.8 (3.1) PAC protocol: 10.2 (1.6) Control: 11.5 (1.7) **Hospital LOS, mean (SD) days** PAC control: 25.2 (3.4) PAC protocol: 19.3 (2.4) Control: 22.2 (2.8)	<0.01 (PAC protocol vs PAC control) <0.10 (PAC protocol vs control) <0.20 (PAC control vs control) <0.05 (PAC protocol vs PAC control) Not given

continued

TABLE 3 *Main results of included RCTs (cont'd)*

Study	Treatment allocation	Withdrawn after randomisation, *n*	Crossovers	Main results	*p* (95% CI)
Valentine *et al.*, 1998[40]	**PAC, *n* = 60** Transfer to ICU, PAC placed followed by 'tune-up' treatment (using predefined end-points used by Berlauk *et al.*[38]) at least 14 h preoperatively **Control, *n* = 60** Not transferred to ICU, CVP catheter placed and no specific preoperative treatment All patients admitted to ICU postoperatively	2	PAC: 0 Control: 2 (excluded from outcome analysis)	**Hospital mortality** PAC: 3/60 (5.0%) Control: 1/60 (1.7%) **ICU LOS (postoperative), mean (SD) days** PAC: 8 (1) Control: 7 (1) **Hospital LOS, mean (SD) days** PAC: 13 (2) Control: 13 (2)	Reported as not significant Reported as not significant Reported as not significant

CVP catheter, central venous pressure catheter (see Appendix 1 for description); IQR, inter-quartile range; LOS, length of stay.

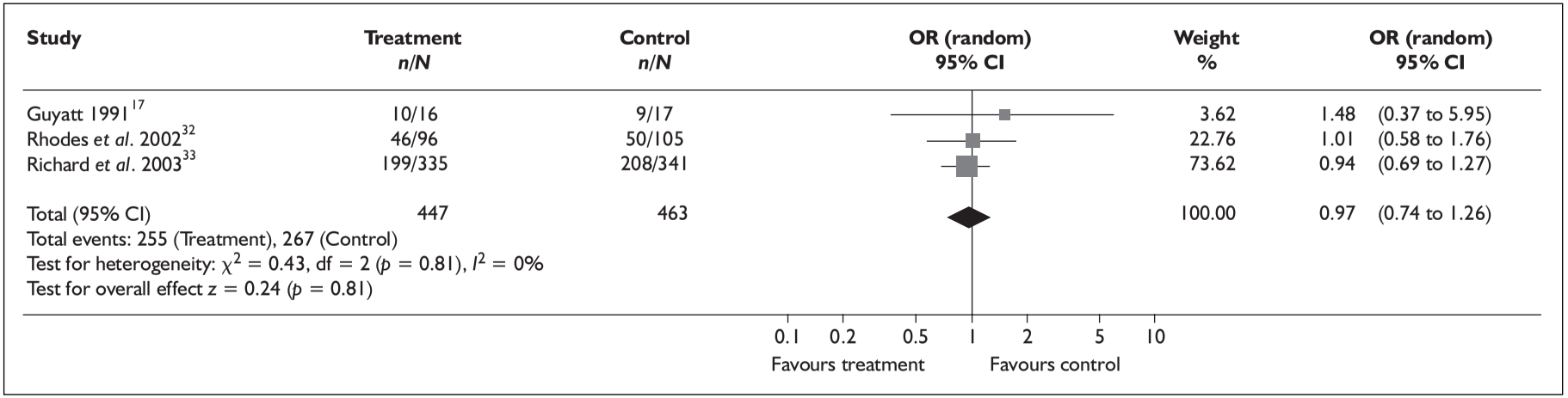


FIGURE 2 *Meta-analysis 1: management with a PAC versus management without a PAC: studies of general ICU patients*

compared with the control group (53%) based on intention-to-treat (*Table 3*). However, of the 17 patients allocated to the control group, eight were subsequently managed with a PAC and, of these, seven (88%) died.

Data from the three studies (910 patients) were pooled to give an OR of 0.97 (95% CI 0.74 to 1.26), comparing management with a PAC to management without a PAC, based on intention-to-treat (*Figure 2*).

Studies of high-risk surgery patients that did not include preoperative optimisation as part of the intervention (n = 3)

One study[34] reported hospital mortality. In this study, one death occurred in the PAC group compared with none in the control group (*Table 3*). Joyce and colleagues[35] examined 30-day mortality and reported no deaths in either treatment group (*Table 3*). Pearson and colleagues[36] reported no difference in ICU mortality between the groups. Overall, there were two deaths, one in the continuous mixed venous oxygen monitoring PAC group and one in the 'control group' who were reassigned following randomisation to be managed with a standard PAC (*Table 3*).

Data from the three studies (368 patients) were pooled to give an OR of 1.10 (95% CI 0.13 to 9.06) comparing management with a PAC to management without a PAC, based on intention-to-treat (*Figure 3*). One study[36] had two PAC groups, which were combined for the pooled analysis.

Studies of high-risk surgery patients that included preoperative optimisation as part of the intervention (n = 5)

Both Valentine and colleagues[40] and Sandham and colleagues[41] reported no significant difference in hospital mortality between the treatment groups (*Table 3*). Bender and colleagues[37] reported no difference in 30-day mortality (*Table 3*). The other studies[38,39] did not specify the type of mortality statistic. Of these, one[38] reported no difference in mortality, whereas the other[39] reported a significant difference in mortality between the PAC plus protocol group and the PAC plus standard care group ($p < 0.01$). However, there was no significant difference in mortality between the control group and either the PAC plus protocol group or the PAC plus standard care group (*Table 3*).

Data from the five studies (2395 patients) were pooled to give an OR of 0.98 (95% CI 0.72 to 1.33) comparing management with a PAC plus preoperative optimisation with usual preoperative care and management without a PAC, based on intention-to-treat. Two studies[38,39] had two PAC groups, which were combined for the pooled analysis (*Figure 4*).

Length of stay in ICU

Six studies[17,34,36,37–39] reported the mean length of stay in ICU for survivors and non-survivors combined. Two studies reported either the mean[17] or the median[32] length of stay in ICU for survivors only. Details, including *p*-values (if reported), are given in *Table 3*. All but one of the studies[39] reported no significant difference in ICU length of stay between the groups. Of note, control group data from Pearson and colleagues' study[36] exclude the 46 patients who were reassigned following randomisation. The mean and standard deviation (SD) values for these patients were reported separately, as follows: reassigned to management with standard PAC ($n = 33$), 2.8 (5.0) days in ICU; reassigned to management with mixed venous oxygen PAC ($n = 13$), 2.6 (3.8) days in ICU. Shoemaker and colleagues[39] reported that patients in the PAC plus standard care group spent significantly longer in the ICU than patients in the PAC plus protocol group ($p < 0.05$) (*Table 3*).

Length of stay in hospital

Five studies[34,37–40] reported the mean and one[41] reported the median length of stay in hospital for survivors and non-survivors combined. Rhodes and colleagues[32] reported the median length of stay for survivors only. None of the studies found a significant difference between the groups (*Table 3*).

Cost

Four studies reported costs of care.[34,36,38,40] These studies were all conducted in the USA and used hospital charges as a measure of costs of care (*Table 4*). None of the studies reported significant differences in the cost of care for patients in the PAC group compared with patients in the control group. In addition to the total hospital charges, Isaacson and colleagues[34] reported professional fees charged by the anaesthesiologists per patient in each group and found that fees were significantly higher per patient in the PAC group than the control group ($p = 0.0001$), as would be expected in a fee-for-service system (*Table 4*).

Discussion

Eleven trials[17,32–41] were identified comparing patients in intensive care managed with and

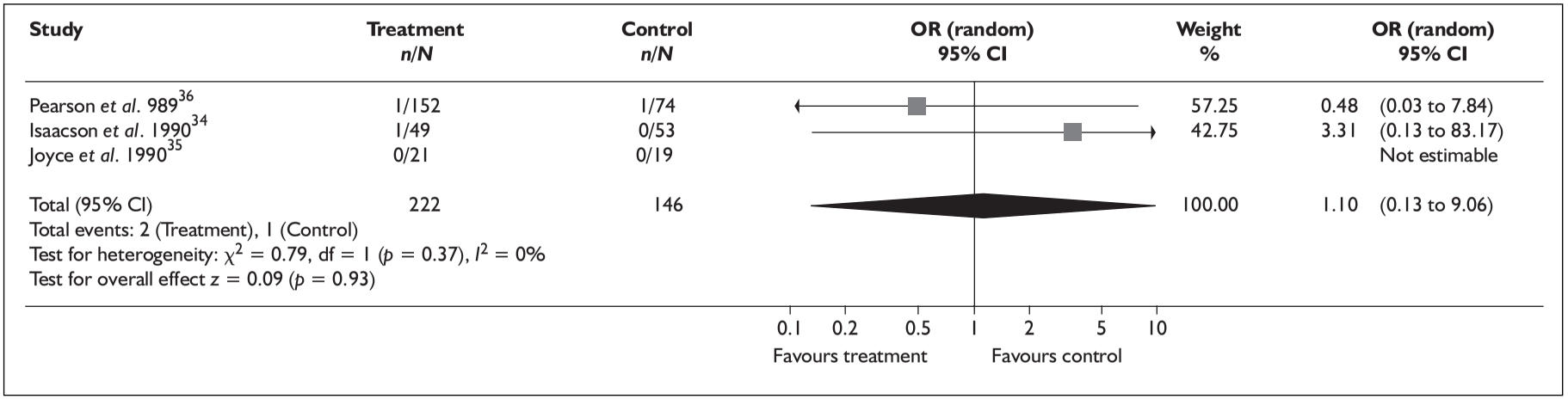


FIGURE 3 *Meta-analysis 2: management with a PAC versus management without a PAC: studies of high-risk surgery patient*

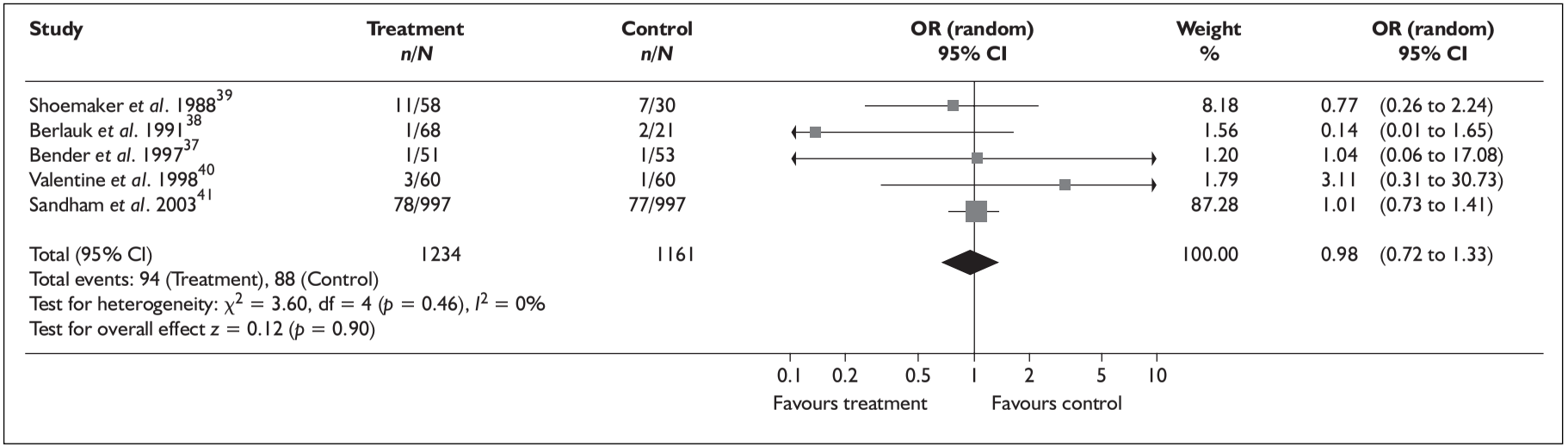


FIGURE 4 *Meta-analysis 3: management with PAC + preoperative optimisation versus management without PAC + usual preoperative care: studies of high-risk surgery patients*

TABLE 4 *Main results of cost evaluations*

Study	Measure	Main results[a]
Studies of high-risk surgery patients: management with a PAC versus management without a PAC		
Isaacson *et al.*, 1990[34]	Total hospital charges per patient, mean (SD)	PAC: $16,680 (9,108) Control: $15,813 (9,028)
	Anaesthesiologist's fee per patient, mean (SD)	PAC: $1,739 (225) Control: $1,551 (252)
Pearson *et al.*, 1989[36]	Total costs (billed to patient), mean (SD)	PAC 1: $855.51 (231) PAC 2: $1128.38 (759) Control: $591.19 (68)[b]
Studies of high-risk surgery patients: management with a PAC + preoperative optimisation versus management without a PAC + usual pre-operative care		
Berlauk *et al.*, 1991[38]	Total hospital charge, mean (SD)	PAC 1: $29,102 (13,207) PAC 2: $23,770 (12,418) Control: $23,386 (12,303)
Shoemaker *et al.*, 1988[39]	Hospital charges, average (not specified)	PAC control: $37,335 PAC protocol: $27, 665 Control: $30,748

[a] Costs in US$.
[b] The costs given for the control group excluded the 46 patients who reassigned after randomisation, which were as follows; reassigned to management with standard PAC (n = 33): mean total cost, $986.38 (578); reassigned to management with mixed venous oxygen PAC (n = 13): mean total cost, $1126.38 (382).

without a PAC. Of these, only three investigated the clinical effectiveness of PACs in the management of general intensive care patients.[17,32,33] The remaining eight studies were of high-risk surgical patients and, of these, five were trials investigating whether preoperative optimisation improves patient outcome.[37–41] Hence placement of a PAC was part of an enhanced package of care that also included admission to ICU preoperatively and 'optimisation' of haemodynamic variables to predetermined goals prior to surgery. Overall, regardless of the patient population studied or inclusion of additional interventions, there was no improvement in patient outcomes as a result of management with a PAC.

Our results are similar to those of previous reviews investigating the effectiveness of PACs.[15,68] Cooper and colleagues[15] included both randomised and non-randomised studies of critically ill patients in intensive care but restricted their selection of studies to those published in English and those where PAC-derived haemodynamic data were used to alter therapy. They found that there was very little evidence from RCTs to support the use of the PAC in clinical practice. Barone and colleagues[68] restricted inclusion of studies in their review to RCTs published in English that described specific therapeutic goals and that were confined to vascular surgery patients. Four papers were identified and included in the meta-analysis, which showed no difference between patients managed with a PAC and those managed without. For the current review, we restricted inclusion of studies to those that had used an RCT design. However, we minimised exclusion criteria; for example, there was no restriction on language or achieving specific therapeutic goals based on PAC-derived data. This was to ensure all RCTs comparing management with and without a PAC involving critically ill patients in intensive care were included in the review. As a result, the studies identified were of different ICU populations with different outcomes and testing different hypotheses. Hence it was not possible to combine data from all studies into one meta-analysis. Therefore, three separate meta-analyses were conducted to investigate the impact of management with a PAC on mortality in different patient populations.

The majority of studies identified in this review were relatively small and were designed to investigate perioperative monitoring, with or without preoperative optimisation of haemodynamics, in patients undergoing high-risk surgery. The main barrier to an effective evaluation of PACs in the management of general intensive care patients has been the lack of equipoise amongst intensive care clinicians, which was one of the main reasons for eligible patients being excluded from the Canadian trial.[17] Our initial search of the literature (to June 2001)

revealed that this was the only RCT of general intensive care patients that had been conducted. It was unfortunately discontinued prematurely because of poor recruitment of patients. The remaining seven studies identified were RCTs involving high-risk surgery patients.

Publication of the non-randomised study by Connors and colleagues in 1996,[18] suggesting that management using a PAC may be harmful to patients, has, it would seem, established clinical equipoise within the critical care community. Since then, in addition to the trial reported below, two more trials involving general intensive care patients have been published and were identified in the updated literature searches in 2003. The first was a single-centre trial in the UK[32] which recruited 201 patients with haemodynamic shock and was intended as a pilot study to inform future RCTs. The second was a large, multi-centre, RCT, conducted in France, which recruited 676 patients with acute respiratory distress syndrome and shock.[33] However, it was not sufficiently powered to detect a 10% absolute difference in 28-day mortality. In addition, another RCT involving high-risk surgery patients has also been published by Sandham and colleagues,[41] which is the largest RCT to date investigating the effectiveness of preoperative optimisation using a PAC.

Few studies have included a cost-effectiveness evaluation as part of an assessment of PACs. We identified four studies,[34,36,38,39] all conducted in hospitals in the USA, that included a cost component. These were all based on the total hospital costs charged to patients. One of the weaknesses of this approach is that specific charges vary across hospitals; for example, patients may or may not be charged for the cost of daily monitoring using a PAC. In general, higher total costs were reported for patients managed with PACs compared with those managed without, although these were not statistically significant.

Conclusions

The initial search of the literature revealed that there was very little RCT evidence on the effectiveness of PACs in clinical practice. One RCT investigating the management of general intensive care patients using a PAC and seven studies investigating management of high-risk surgery patients were identified. These were all small, mainly single-centre studies. In addition, although some studies included an evaluation of costs of care, again these were small studies, which were conducted in the USA and were based on hospital charges. This review identified a clear need for a large, multi-centre RCT of the clinical and cost-effectiveness of PACs in the management of patients in general intensive care. The current RCT was therefore designed to address a number of issues, including the range of patients managed in intensive care with a PAC and the lack of consensus within the critical care community regarding management protocols. The trial is described in detail in Chapter 3.

Chapter 3

Randomised controlled trial to evaluate the clinical effectiveness of pulmonary artery catheters in patient management in intensive care

Aim

The aim of the RCT was to test the hypothesis that hospital mortality is decreased in critically ill patients in adult ICUs who are managed with a PAC compared with those who are not.

Design and development of the trial protocol

There were a number of potential problems that had to be addressed in the design of the trial. An important issue was a lack of consensus among critical care clinicians as to the indications for insertion of a PAC and how patients should be subsequently managed following its placement, including administration of fluids and vasoactive drugs and target levels for blood pressure and cardiac output. Also, PACs were widely used in ICUs in the UK across a range of patients and by doctors and nurses with varying levels of expertise. Given the lack of consensus, it was felt inappropriate to introduce a management protocol for the trial, particularly as it would have become an evaluation of the PAC plus the protocol rather than the PAC itself. Furthermore, the results would not have been generalisable outside the patient group treated according to the protocol. Therefore, a multi-centre, pragmatic RCT design was adopted to investigate the effectiveness of PACs as they are currently used in the UK. In brief, a study design was chosen to answer the question, 'What would be the effect on hospital mortality of removing PACs from clinical use?'

The UK critical care community, in addition to international experts, were consulted and asked to provide input into the development of the trial protocol. In 2000, representatives from all general, adult ICUs in the UK were invited to a Collaborators' Meeting to discuss the draft trial protocol. One of the main talking points of the meeting was whether or not less invasive monitoring devices should be allowed as an alternative to the PAC. Such devices have become increasingly popular and a large proportion of ICUs were now using them, either as an alternative or as an adjunct to the PAC. At least 50% of clinicians argued that to participate in the trial, they would have to be allowed the option to use alternative devices to measure cardiac output in patients allocated to the control group, that is, those not to be managed with a PAC. In other words, the PAC itself would be 'on trial'. Others argued that the trial should be an evaluation of the PAC versus no other form of cardiac output monitoring, thus examining the impact of monitoring cardiac output. These views were incorporated into the design of the trial, and participating ICUs elected to be in one of two strata as follows:

- stratum A: no option to use alternative devices to measure cardiac output in control group patients
- stratum B: option to use alternative devices to measure cardiac output in control group patients.

The alternative devices available to monitor the cardiovascular system and measure cardiac output are described in Appendix 1. At the start of the trial, it was anticipated that most ICUs using devices other than the PAC to measure cardiac output would be using pulse contour or trans-oesophageal Doppler devices. The use of central venous pressure (CVP) catheters is ubiquitous in intensive care patients and was permitted in an unrestricted manner for all patients in the trial. Echocardiography is a technique used for diagnostic rather than monitoring purposes and was also permitted in an unrestricted manner in the trial.

Methods

The final trial protocol was approved by the London Multi-centre Research Ethics Committee (MREC) and each participating hospital's Local Research Ethics Committee (LREC).

ICU recruitment

A database of all adult general ICUs in the UK has been constructed by ICNARC using The Directory of Critical Care (formerly The Directory of Emergency and Special Care Units) produced and published by CMA Medical Data, and through direct contact with ICUs. A postal invitation to participate in the trial was sent to the Clinical Director at every general, adult ICU listed in this database (n = 263). Follow-up letters were sent to non-responders. ICUs that expressed an interest in participating were contacted by telephone and visited by a member of the study team. A prerequisite for an ICU to participate in the trial was that all consultants should agree to include all eligible patients and to abide by randomisation to minimise selective enrolment and crossover of patients.

A Local Investigator, who was responsible for the conduct of the trial locally, was identified at each ICU. Another contact, usually a nurse or a data collection clerk, was also identified to act as an additional link between the ICU and the Trial Coordinating Centre. Once approval had been obtained from the relevant LREC and the hospital's Research and Development Department, one of the Trial Research Nurses visited the ICU. The visit typically involved a presentation to the staff describing the background, aims and methods of the trial followed by discussion and questions. The Trial Research Nurse checked that all trial materials were on site and went through the enrolment and randomisation procedures and the data collection forms with the ICU staff. Follow-up visits were arranged as necessary to monitor progress, maintain awareness of the trial and encourage ongoing participation.

Newsletters

During the course of the trial, monthly newsletters were sent to all ICUs in the UK to keep them informed of progress, to encourage participation and to remind Local Investigators to enrol all eligible patients.

Collaborators' Meetings

During the patient recruitment phase of the trial, representatives from all participating ICUs were invited to two Collaborators' Meetings. These were to keep collaborators informed of study progress, to encourage continued participation and to provide an opportunity to discuss any issues with the conduct of the trial locally. An additional Collaborators' Meeting was convened to present the results of the PAC-Man Study to representatives from participating ICUs.

Support costs

The ICUs were offered no financial incentives to take part in the trial but were reimbursed £15 per patient recruited as a contribution towards the administration costs of the trial.

Trial participants

The trial population comprised general intensive care patients fulfilling the eligibility criteria outlined below.

Inclusion and exclusion criteria

Patients were eligible for inclusion in the trial if they were intensive care patients deemed by the responsible treating clinician to require management with a PAC. Patients were excluded if they were less than 16 years of age, were admitted to the ICU electively prior to surgery for preoperative optimisation, had a PAC already *in situ* on admission to the ICU, had previously been entered into the trial or had been declared brain dead following brain stem death testing, with a PAC being placed for organ support prior to donation.

Patient consent

Where possible, patients were asked to give their informed consent prior to randomisation. The Local Investigator discussed the trial with the patient and gave them an information sheet to read (Appendix 4). The patient then signed a consent form indicating their agreement to take part (Appendix 5). However, in most cases this was not possible because PACs are frequently used in the most severely ill patients who have altered consciousness. In these cases, where possible, the Local Investigator discussed the trial with the patient's relatives and gave them an information sheet explaining that although they could not provide consent on behalf of the patient, they could offer an opinion as to whether the patient would object to taking part in medical research (Appendix 6). The relative was then asked to provide signed assent in the form of a written agreement, prior to randomisation (Appendix 7). If the relatives could not be contacted, the patient was randomised and signed assent was obtained from the relative as soon as possible, retrospectively. If the patient regained mental competency, the patient was informed of their enrolment into the trial and given an information sheet to read (Appendix 8). The patient was then asked to sign a consent form indicating agreement to the use of their data in the trial analysis (Appendix 5).

Randomisation and allocation

Randomisation was carried out via an independent, central, 24-hour telephone randomisation service.

A study investigator was available 24 hours per day to answer questions relating to enrolment and randomisation. To randomise a patient, the Local Investigator telephoned the randomisation centre and provided basic identification details, confirmed the patient's eligibility for the trial and provided data for minimisation. Patients were given a unique study number and were assigned on a 1:1 allocation to be managed either with or without a PAC. Treatment was assigned by the minimisation method to balance across the following four factors: individual ICU; age group (16–44 years, 45–64 years, 65 years and above); the presumptive clinical syndrome (acute respiratory failure, multi-organ dysfunction, decompensated heart failure, other clinical syndrome); and surgical status (elective surgical, emergency surgical, non-surgical).

Patients allocated to, according to local practice, be managed with a PAC had the catheter placed as soon as possible following randomisation. The PAC remained in place for as long as the responsible treating clinician considered necessary. Patients allocated to the control group were managed without a PAC with the option to use alternative cardiac output monitoring technologies in ICUs that elected to be in stratum B. In both groups, clinical management following randomisation was at the discretion of the responsible treating clinician. Participating ICUs maintained a screening log of eligible patients not enrolled into the trial, recording the date of eligibility for the trial, date of birth, sex and reason for exclusion.

Sample size calculation

The original sample size calculation was based on data kindly supplied by the Scottish Intensive Care Society Audit Group (personal communication) in 1999 from their database containing details of all patients admitted to Scottish ICUs. The data suggested a hospital mortality of 50% for patients managed with a PAC. Since it was felt that a 5% change in hospital mortality would represent a clinically important finding, we wished to be able to detect a reduction in hospital mortality from 55%, for patients not managed with a PAC, to 50% (with the potential risk of a rise to 60%) based on a 5% level of statistical significance for a two-sided test. It was calculated that a sample of 4184 patients (2092 in each arm) would have 90% power to detect a difference of this size. We allowed for a 4% non-compliance rate in the PAC group and 8% in the control group and a 5% loss to follow-up, which increased the required sample size to 5673.

At the point where we estimated our original sample size, approximately 18% of admissions to UK ICUs were being managed with a pulmonary artery catheter.[70] However, the results of the Connors and colleagues' study (39% increased odds in hospital mortality associated with management with a PAC)[18] caused a precipitous reduction in the use of PACs (recent unpublished data suggest that approximately 3% of admissions are now managed with a PAC) and a rapid uptake of less invasive cardiac output monitoring technologies. The consequence of this was slow patient recruitment to the trial. In response to this, the Trial Steering Committee agreed that the Trial Statistician should examine the characteristics (severity of illness) and actual hospital mortality of control group patients recruited at that point (n = 147). These results, combined with anecdotal evidence from clinicians, strongly suggested that clinical practice for managing patients with PACs had changed with their use being restricted to fewer and more severely ill patients. Indeed, the actual hospital mortality for these patients was much higher, 69% (95% CI 61 to 77%) than that originally incorporated (50%) into the sample size calculation. Despite this change in clinical practice, the hypothesis being tested in the RCT remained valid. The Trial Steering Committee decided to recalculate the sample size, increasing the clinically important difference from 5 to 10%. This decision was based on the changes in clinical practice, the higher actual hospital mortality and pragmatism, that is, an achievable sample size. The reduction in relative hospital mortality thus changed from 10 to 14.5%. It was calculated that a sample of 992 patients (496 in each arm) would have 90% power to detect a 10% change in hospital mortality based on a 5% level of significance for a two-sided test. We allowed for a 4% non-compliance rate in the PAC group and 8% in the control group, which increased the sample size to 1281 patients. Since the follow-up ended at hospital discharge, allowing a 5% loss to follow-up was considered unnecessary. We felt confident that the results of the PAC-Man Study would remain meaningful in light of the results of Connors and colleagues' study.[18]

Changes to the trial protocol

There were two amendments to the original trial protocol approved by the MREC on 12 March 2001. The first amendment, on 27 September 2002, reflected the change to the sample size calculation and is described above. The second amendment dealt with the issue of patients who regained consciousness following their critical illness but did not regain mental competency to be able to provide informed consent. The exclusion

criteria (described above) were amended in order to exclude patients admitted to the ICU where the specific reasons for admission, or other circumstances, suggested that they might later be unable to give consent on recovery; for example, mental handicap or learning difficulties. The patient consent procedure was also amended so that for a patient who regained consciousness but did not regain sufficient mental competency to understand the purpose and consequences of participating in the study nor, in the opinion of the Local Investigator (ICU Consultant), was likely to do so, a 'Patient Incapacity to Provide Retrospective Consent' form (Appendix 9) was completed and a copy sent to the Chair of the LREC. Following notification to the LREC, and in the absence of any objection from it, data collection continued and the data were submitted for inclusion in the trial analysis without the patient's consent unless or until they regained mental competence. The patient's next of kin, where available, were asked if they knew of any reason why the patient would not want their data to be used in this way. If a reason was identified, the patient was excluded from the trial. The LRECs were informed of these amendments to the trial protocol following approval by the MREC.

Data

Given the limited resources available to ICUs for the conduct of research, data collection for the trial was kept to a minimum and restricted where possible to data that are recorded routinely in most ICUs (Appendix 10).

At study entry, prior to randomisation, baseline data recorded included sex, date of birth, source of admission (surgical/non-surgical) and presumptive clinical syndrome. At the time of randomisation, the primary reason for wanting to manage the patient with a PAC and the current organ monitoring/support, based on the criteria used for the Augmented Care Period (ACP) dataset[71] (Appendix 11), were collected. In addition, raw clinical data for the Sepsis-related Organ Failure Assessment (SOFA) score[72] (Appendix 12) were collected to provide information on the patient's severity of illness at the time they were being considered for a PAC. During the first 24 hours in the ICU, raw clinical data for the Acute Physiology And Chronic Health Evaluation version II (APACHE II) severity scoring system[73] (Appendix 13) were collected.

Post-randomisation use of alternative cardiac output monitoring devices and type of organ monitoring/support based on the criteria used for the ACP dataset[71] (Appendix 11) were collected daily during the patient's stay in the original recruiting ICU. At discharge from the original recruiting ICU, the patient's outcome (alive/dead) was recorded and the date and time of discharge or death were recorded. Patients were followed up until discharge from, or death in, an acute hospital.

For patients allocated to the PAC group, complications occurring as a direct result of insertion of the PAC, changes in management within the first 2 hours as a direct result of PAC-derived data, duration of management with the initial PAC and overall management with a PAC were also recorded.

Primary and secondary outcome measures

The primary outcome was hospital mortality, defined as death from any cause before ultimate discharge from an acute hospital. ICU mortality, defined as death from any cause before discharge from the original recruiting ICU, and mortality at 28 days post-randomisation were also recorded for comparability with other studies. Secondary outcomes were the length of stay in the original ICU, total length of stay in an acute hospital and organ-days of support in the original recruiting ICU.

Follow-up

All patients were followed up to hospital discharge, the study end-point. Enrolment of patients into the trial ended on 31 March 2004. Data collection, including follow-up of patients, continued until 30 June 2004. Data on patients who remained in an acute hospital at this point were censored.

Data preparation

All data were double entered and validated in a relational database (Microsoft Access 2000) and wherever possible variables were given numeric codes. Data were exported to the statistical package Stata 8.2 (StataCorp, College Station, TX, USA) for statistical analysis.

Data integrity

All data were checked for inconsistencies, for physiological variables outside predetermined ranges and for missing data, which were followed up with Local Investigators.

Data analysis

All the main analyses used the intention-to-treat principle, considering the groups as randomised, and followed a predetermined statistical analysis plan.

Representativeness of participating ICUs

Participating ICUs were compared with adult general ICUs participating in the ICNARC Case Mix Programme (CMP), the national comparative clinical audit of patient outcome from intensive care.[74] Currently, 73% (n = 181) of adult general ICUs in England, Wales and Northern Ireland take part in the CMP (Scotland has its own performance assessment programme). Comparison was by hospital type (university, university affiliated, non-university) and size of unit, that is, number of critical care beds.

Representativeness of participants

Eligible participants and non-participants were reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement.[75] Trial participants were compared with eligible non-participants (recorded in the screening logs at participating ICUs) for age and sex.

Comparability of the groups

The two groups (PAC and control) were compared at entry for general baseline characteristics [age, sex and stratum, (A or B)], for baseline characteristics at the time of admission to ICU [surgical status – medical, elective surgery, emergency surgery, APACHE II acute physiology score (APS), APACHE II score, risk of death predicted by APACHE II and confirmed infection) and for baseline characteristics at the time of randomisation (time in hours to randomisation post-ICU admission, major presumptive clinical syndrome – acute respiratory failure, multi-organ dysfunction, decompensated heart failure and other, and SOFA score). Numbers and proportions or means with SDs were reported as appropriate in each group. In line with current recommendations, statistical tests comparing baseline characteristics between the two groups were not performed.[75,76]

Main analyses

The numbers of deaths in each group were compared with Fisher's exact test. Survival times were compared with Kaplan–Meier curves and tested with a log-rank test, for all patients and by stratum. For the purpose of in-hospital survival analyses, patients discharged from an acute hospital alive were assumed to survive until the end of the follow-up period (3 months after patient recruitment ended). Data from patients still in an acute hospital at this point were censored. The hazard ratio for management with a PAC compared with no PAC was calculated from a Cox proportional hazards model, both with and without adjustment for prognostic factors (age, sex, surgical status, major presumptive clinical syndrome at time of randomisation, SOFA score at time of randomisation and APACHE II score during the first 24 hours in ICU).

Secondary analyses

Hospital mortality was also assessed in predetermined subgroups based on option or not to use alternative cardiac output monitoring technologies in the control group, APACHE II-predicted risk of hospital death, presumptive clinical syndrome and historic frequency of PAC use in the participating ICU derived from the 1998 Audit Commission survey.[70] The subgroups were compared by testing the interaction with treatment effect in the adjusted Cox proportional hazards model. For APACHE II-predicted risk of hospital death, predicted log odds of death were entered as a linear term in the Cox model.

A secondary analysis to account for non-compliance (PAC patients not receiving PAC) and contamination (control patients receiving PAC) was undertaken using the methods described by Cuzick and colleagues.[77] The treatment effect in compliers was estimated as the relative risk with 95% CI.

Secondary outcomes

Differences between the two groups in the median length of stay in the original recruiting ICU and in an acute hospital were compared using the Wilcoxon rank-sum test. A bootstrap t-test[78] was undertaken to estimate the difference in mean length of stay in ICU and an acute hospital between the two groups. Organ-days of support were calculated as the sum of the days of individual organ support. For example, one calendar day where three individual organs were supported was equivalent to three calendar days where one individual organ was supported. The mean organ-days of support were compared between the two groups using a bootstrap t-test.

Complications and management of patients in the PAC group

Complications and changes in management following insertion of the PAC were described and the numbers (%) tabulated. The duration of management with the initial PAC was calculated from the dates and times of insertion and removal. The overall number of days of management with a PAC following randomisation was calculated from daily follow-up data.

Use of alternative cardiac monitoring devices

The use of alternative cardiac output monitoring devices was reported by treatment group

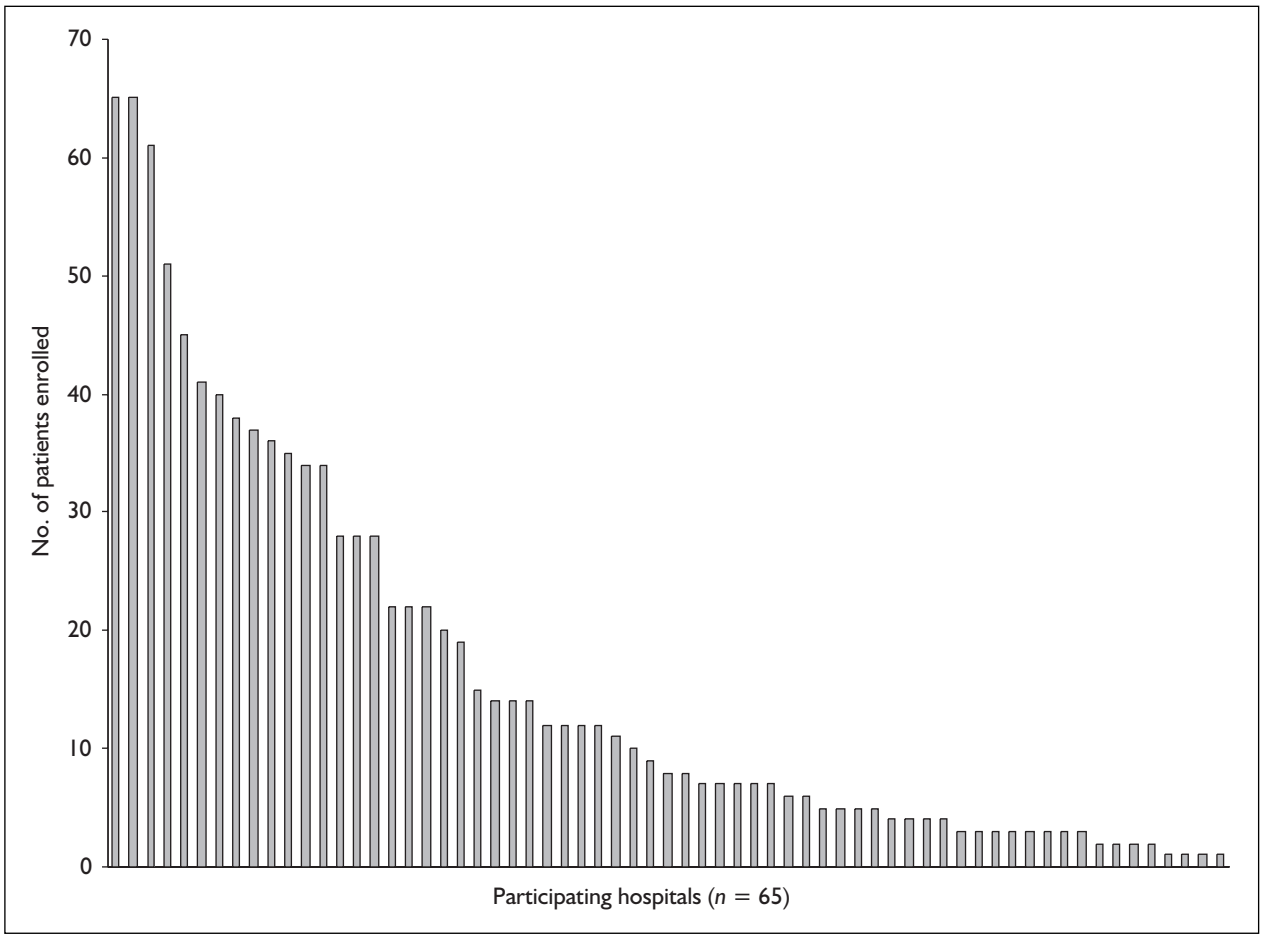


FIGURE 5 *Patient recruitment by ICU*

(PAC and control) and by stratum, including non-compliance within strata.

An independent Data Monitoring and Ethics Committee conducted two interim safety analyses and at both points recommended that the trial continue.

Results

Recruitment of ICUs

Recruitment of ICUs took place between July 2000 and December 2003. Ninety-seven ICUs expressed an interest in taking part in the trial and were sent an LREC application pack. Of these, 79 ICUs sought and gained approval from their LRECs. The remaining ICUs decided not to participate for a variety of reasons, most frequently because there was lack of equipoise within the ICU or there were limited resources available for research activities. A total of 65 ICUs recruited one or more patients (*Figure 5*). Of these, 55 were in England, four in Northern Ireland, three in Scotland and three in Wales. The characteristics of participating ICUs were similar to those of ICUs in the CMP. Thirteen (20%) of the participating ICUs were located in university hospitals, eight (12.3%) in university-affiliated hospitals and 44 (67.7%) in non-university hospitals (*Table 5*). The number of beds in an individual ICU ranged from four to 22 beds. Ten ICUs (15.4%) had five beds or less, 40 (61.5%) had between six and 10 beds, 14 (21.5%) had between 11 and 15 beds and one (1.5%) had 22 beds (*Table 6*).

Twenty-two (34%) ICUs opted to be in stratum A and 43 (66%) in stratum B. ICUs were not asked to give reasons for their choice of stratum. Ten of the 13 ICUs located in university hospitals opted to be in stratum B. Of the 22 ICUs in stratum A, five (two located in university hospitals and three in non-university hospitals) acquired an alternative cardiac output monitoring device during the patient recruitment period and crossed over to stratum B (*Table 7*). Patients in these units were considered to be in stratum A or B depending on the date on which they were randomised, that is, before or after the crossover.

TABLE 5 *Location of ICUs – hospital type*

Type of hospital	PAC-Man *n* (%)	CMP[a] *n* (%)
University	13 (20.0)	41 (22.7)
University-affiliated	8 (12.3)	32 (17.7)
Non-university	44 (67.7)	108 (59.7)
Total	65 (100)	181 (100)

[a] CMP, Case Mix Programme, the national comparative clinical audit of patient outcome (England, Wales and Northern Ireland).

TABLE 6 *Size of ICU*

Reported number of beds	PAC-Man *n* (%)	CMP[a] *n* (%)
≤ 5	10 (15.4)	34 (18.8)
6–10	40 (61.5)	105 (58.0)
11–15	14 (21.5)	31 (17.1)
≥ 16	1 (1.5)	11 (6.1)
Total	65 (100)	181 (100)

[a] CMP, Case Mix Programme, the national comparative clinical audit of patient outcome (England, Wales and Northern Ireland).

TABLE 7 *Characteristics of ICUs by stratum*

Hospital type	Stratum A *n* (%) (*n* = 17)	Stratum B[a] *n* (%) (*n* = 48)
University	1 (5.9)	12 (25.0)
University-affiliated	3 (17.6)	5 (10.4)
Non-university	13 (76.5)	31 (64.6)
Size of ICU		
≤ 5 beds	5 (29.4)	5 (10.4)
6–10 beds	11 (64.7)	29 (60.4)
11–15 beds	1 (5.9)	13 (27.1)
≥ 16 beds	0	1 (2.1)

[a] Includes the five ICUs that swapped stratum during the patient recruitment period.

Recruitment of trial participants

A total of 1263 patients were identified as being eligible for participation in the trial between 15 October 2001 and 31 March 2004 (*Figure 6*). Of these, 222 (17.6%) were not enrolled into the trial. The most frequently reported reason for not enrolling eligible patients were that the clinician refused to randomise the patient because of loss of equipoise (49.5%) or that the relatives refused on the patient's behalf (21.2%) (*Table 8*). The excluded patients were similar with regard to mean age and sex to patients who were enrolled into the trial (*Table 9*).

Hence, 1041 patients were randomised and allocated to either the control group (n = 522) or to the PAC group (n = 519). Of the 522 patients allocated to the control group, 24 (4.6%) were subsequently managed with a PAC. In all but one case (due to staff error), this was due to loss of equipoise. Of the 519 patients allocated to the PAC group, 33 (6.4%) were subsequently managed without a PAC. Of these, insertion of the PAC was unsuccessful in 13 (2.5%) cases, the clinical condition either deteriorated or improved following randomisation in 14 (2.7%) cases such that a PAC was considered inappropriate and in a further six cases (1.2%) there were safety concerns (coagulopathy). There were no losses to follow-up, but 14 patients in the control group and 13 in PAC group were excluded from the trial analysis because either the patient withdrew consent on

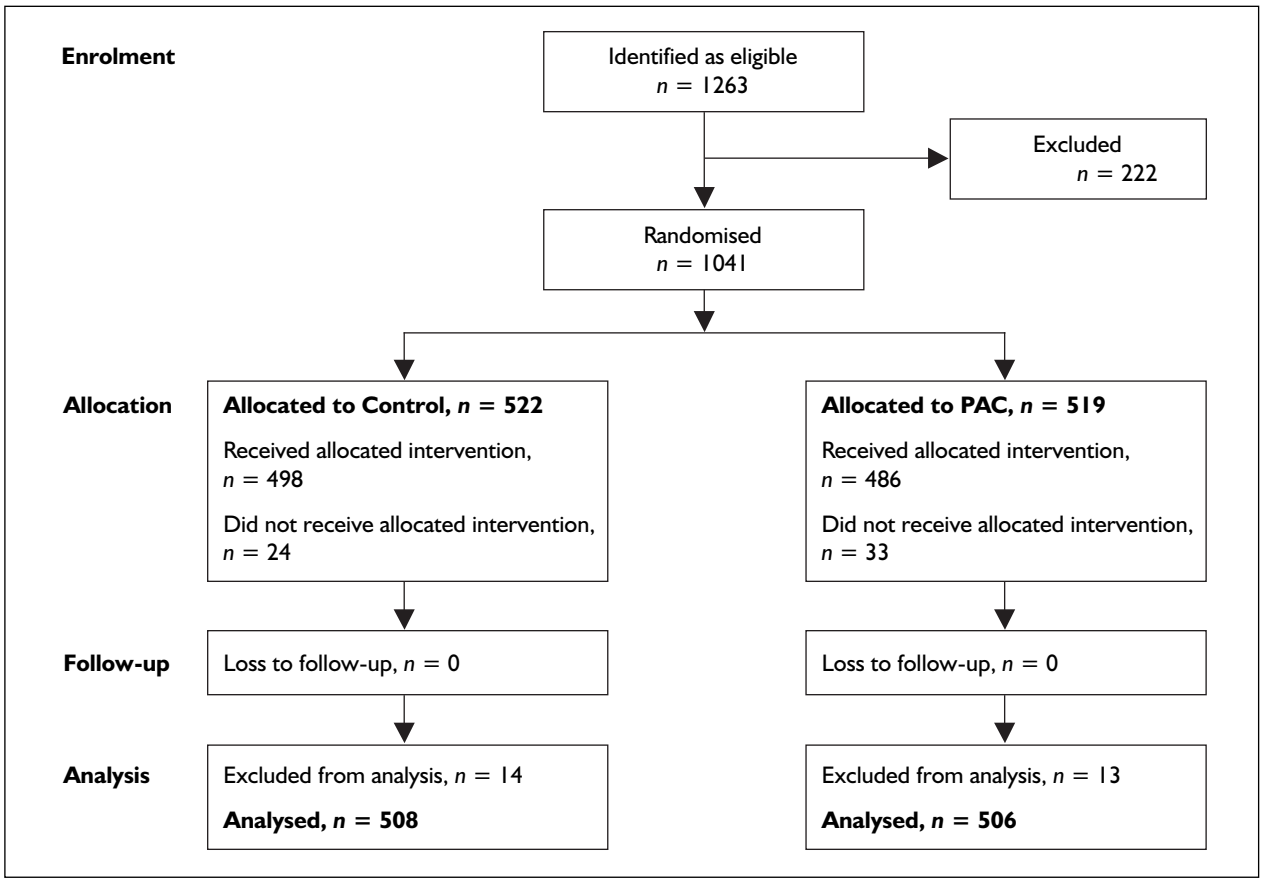


FIGURE 6 *Patient recruitment*

TABLE 8 *Eligible patients excluded from the study* (n = *222)*

Reason for exclusion	***n* (%)**
Clinician refused, no equipoise	110 (49.5)
Relative refused	47 (21.2)
Relatives not approached	7 (3.2)
Change in clinical condition[a]	7 (3.2)
Practical issue[b]	25 (11.3)
Staff error[c]	16 (7.2)
No reason given	10 (4.5)

[a] The patient's clinical condition either deteriorated or improved.
[b] Lack of monitoring equipment/study materials/necessary clinical expertise, failure of randomisation service/study recruitment suspended by unit.
[c] Staff forgot to randomise/misunderstood study protocol.

TABLE 9 *Characteristics of excluded patients*

	Eligible – enrolled *n* = 1014[a]	**Eligible – excluded *n* = 222[b]**
Male, *n* (%)	591 (58.3)	114 (51.4)
Female, *n* (%)	423 (41.7)	96 (43.2)
Age (years), mean (SD)	65.0 (13.7)	63.9 (15.8)

[a] Excludes 27 patients who withdrew from the study following randomisation.
[b] 12 patients sex not recorded, 98 patients some or all data required to calculate age not recorded.

TABLE 10 *Most frequently reported diagnoses on admission to ICU for all participants*

Diagnosis on admission to ICU	*n* (%)
Pneumonia	203 (20.0)
Septicaemia/septic shock	106 (10.5)
Left ventricular failure/cardiogenic shock/cardiogenic pulmonary oedema	69 (6.8)
Non-traumatic large bowel perforation or rupture	52 (5.1)
Aortic or iliac dissection, aneurysm or rupture	48 (4.7)
Acute myocardial infarction	36 (3.6)
Acute renal failure	30 (3.0)
Acute pancreatitis	25 (2.5)
Duodenal perforation due to ulcers	19 (1.9)
Non-cardiogenic pulmonary oedema (ARDS)	16 (1.6)
Large bowel tumour	14 (1.4)
Leaking large bowel anastomosis	14 (1.4)
Bleeding duodenal ulcer, duodentitis or duodenal diverticulum	10 (1.0)
Hypovolaemic shock	10 (1.0)

ARDS, acute respiratory distress syndrome.

recovery or the relatives withdrew agreement following randomisation. Data from a total sample of 1014 patients were analysed (*Figure 6*).

Trial participants at baseline

Two-thirds (66.3%) of the participants were medical (non-surgical) patients. Overall, the most frequent diagnoses on admission to ICU were pneumonia (n = 203, 20.0%) and septic shock or septicaemia (n = 106, 10.5%) (*Table 10*). The characteristics of participants at baseline, by treatment group, are detailed in *Table 11*. Participants in the two groups had similar characteristics, including severity of illness during the first 24 hours in the ICU and at the time of randomisation using the APACHE II score[73] (Appendix 12) and SOFA score[72] (Appendix 11), respectively. The median time to randomisation post-ICU admission was also similar for the two groups. For the PAC group, the median time from randomisation to device insertion was 1.7 hours (interquartile range 1.1–2.7 hours). The most frequently reported reason for wanting to manage the patient with a PAC was to guide inotropic/vasoactive drug treatment in a patient already receiving these drugs, 73.5 and 70.9% of patients in the PAC and control groups, respectively (*Table 11*).

Primary outcome

All patients were followed up until discharge from an acute hospital, except for one patient who was still in hospital 3 months after the end of recruitment and whose data were censored at this point. Hospital mortality was similar in the two groups, 65.7% in the control group and 68.4% in the PAC group (*Table 12*), as was in-hospital survival to 90 days (*Figure 7*). The hazard ratio for PAC compared with control, adjusting for prognostic factors, was 1.09 (95% CI 0.94 to 1.27) (*Table 13*). There was no evidence to reject the hypothesis of proportionality (p = 0.54). The relative risk for PAC compared with control adjusting for non-compliance and contamination[77] was 1.05 (95% CI 0.94 to 1.15) (*Table 14*). In the predetermined subgroups, no differences in treatment effect on hospital mortality were observed (*Table 15*).

Secondary outcomes

Table 16 details both the mean and median values for length of stay in the original recruiting ICU, the total length of stay in an acute hospital and the organ-days of support in the original recruiting ICU for survivors and non-survivors. No differences were observed between the two groups.

Complications as a result of PAC insertion

One or more direct complications were reported in 46 (9.5%) of 486 patients in whom PAC insertion was attempted. The most frequent complications reported were haematoma at the insertion site (n = 17, 3.5%), arterial puncture (n = 16, 3.3%) and arrhythmias requiring treatment within 1 hour of insertion [n = 16, 3.3% (one of which was a cardiac arrest)]. Other complications included pneumothorax (n = 2), haemothorax (n = 1) and retrieval of a 'lost' insertion guide wire from the femoral vein and inferior vena cava (n = 2).

TABLE 11 *Patients' characteristics*

Characteristic	Treatment group	
	Control (*n* = 508)	**PAC (*n* = 506)**
Minimised by:		
ICU, *n* (%):		
A (no option of alternative cardiac output monitoring device)	107 (21.1)	105 (20.8)
B (option of alternative cardiac output monitoring device)	401 (78.9)	401 (79.2)
Age (years), mean (SD)	65.3 (13.1)	64.7 (14.3)
Surgical status, *n* (%):		
Non-surgical	340 (66.9)	332 (65.6)
Elective surgery	32 (6.3)	32 (6.3)
Emergency surgery	136 (26.8)	142 (28.1)
Major presumptive clinical syndrome, *n* (%):		
Acute respiratory failure	66 (13.0)	68 (13.4)
Multi-organ dysfunction	337 (66.3)	328 (64.8)
Decompensated heart failure	56 (11.0)	55 (10.9)
Other	49 (9.6)	55 (10.9)
Other:		
Sex, *n* (%):		
Female	204 (40.2)	219 (43.3)
Male	304 (59.8)	287 (56.7)
1st 24-hour APACHE II APS, mean (SD)[a]	18.0 (6.4)	17.3 (6.3)
1st 24-hour APACHE II score, mean (SD)[a]	22.7 (6.5)	22.1 (6.6)
APACHE II risk of death, median (IQR)[b]	0.39 (0.23–0.55)	0.37 (0.23–0.57)
Likely infection on ICU admission, *n* (%)[c]	273 (53.7)	300 (59.3)
Time (hours) to randomisation post-ICU admission, median (IQR)[d]	15.3 (4.3–34.8)	16.2 (5.8–42.0)
SOFA score at time of randomisation, mean (SD)	8.6 (2.7)	8.6 (2.7)
Main reason for wishing to manage patient with a PAC, *n* (%):		
To guide inotropic/vasoactive drug treatment in a patient not yet receiving these drugs	39 (7.7)	41 (8.1)
To guide inotropic/vasoactive drug treatment in a patient already receiving these drugs	358 (70.9)	371 (73.5)
To guide fluid/diuretic/haemofiltration treatment	50 (9.9)	50 (9.9)
To guide treatment of oliguria	21 (4.2)	10 (2.0)
To guide treatment of a metabolic acidosis	21 (4.2)	19 (3.8)
To diagnose and/or guide treatment of the cause for failure to wean from mechanical ventilation	3 (0.6)	3 (0.6)
Other diagnostic reasons	13 (2.6)	11 (2.2)

[a] Excludes 23 patients in the control group and 23 in the PAC group who stayed in ICU <8 h.
[b] Excludes 44 patients in the control group and 47 in the PAC group who stayed in ICU <8 h or who had incomplete data.
[c] Likely infection = strongly suggestive by evidence, or laboratory-confirmed infection.
[d] Excludes 13 patients where date and/or time of randomisation and/or admission missing.

TABLE 12 *Crude hospital mortality by treatment group*

Treatment group	Status at hospital discharge[a]		Total
	Alive, *n* (%)	**Dead, *n* (%)**	
Control	174 (34.3)	333 (65.7)	507
PAC	160 (31.6)	346 (68.4)	506
Total	334 (33.0)	679 (67.0)	1013

[a] One patient remained in hospital at the end of the follow-up period.
Fisher's exact test: $p = 0.385$.

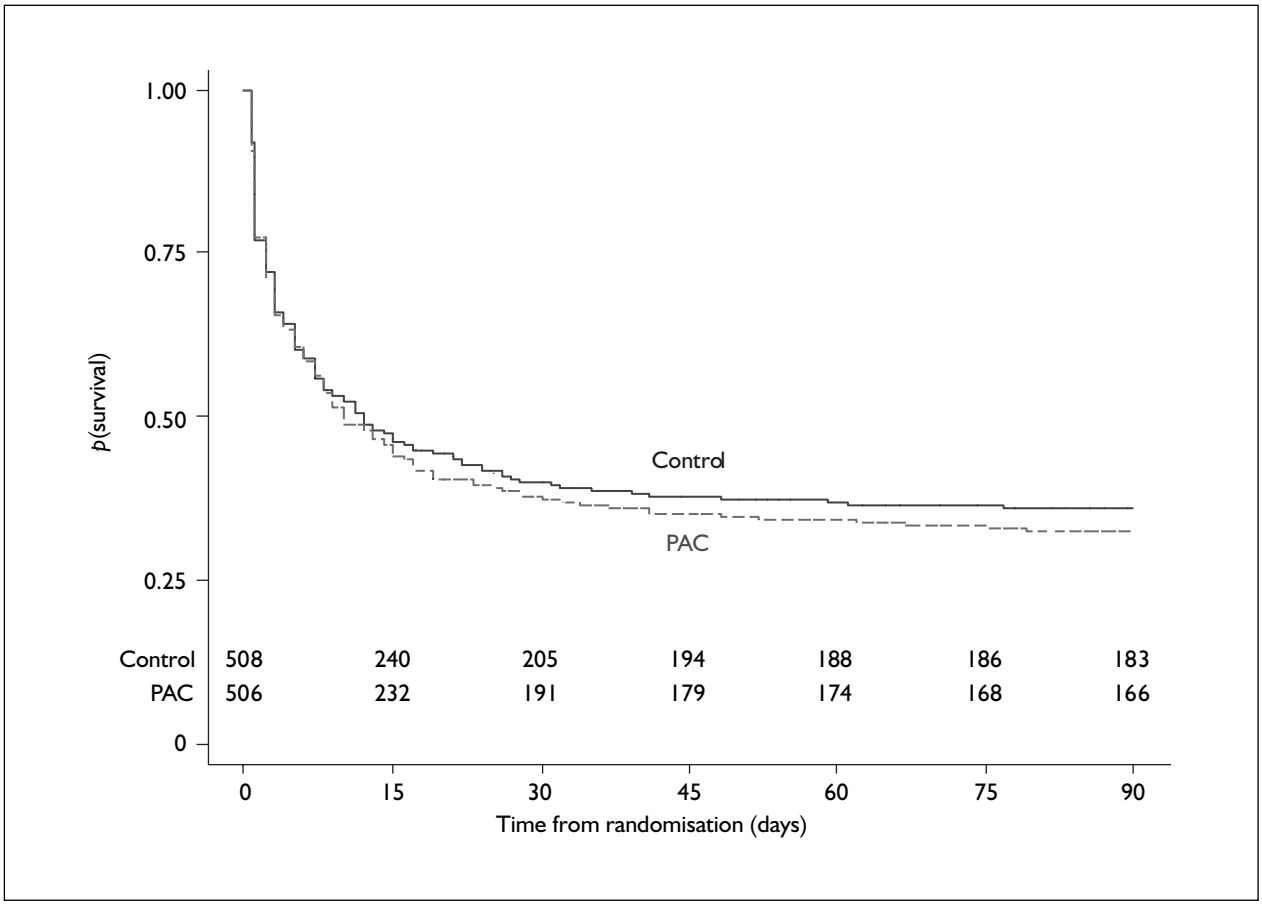


FIGURE 7 *Kaplan–Meier survival curves for in-hospital mortality by treatment group. Patients discharged alive from hospital before 90 days assumed to still be alive at 90 days. Numbers at foot of figure are numbers at risk in each treatment group. Plot truncated at 90 days. There were 12 deaths later than 90 days (5 PAC, 7 control). Log-rank test (stratified by stratum):* $\chi^2(1) = 0.77$, $p = 0.381$.

TABLE 13 *Cox proportional hazards model*

Model	**Hazard ratio (95% CI) PAC vs control**	***p*-Value**
Unadjusted	1.07 (0.92 to 1.24)	0.40
Adjusted[a]	1.09 (0.94 to 1.27)	0.25
[a] Adjusted for age, sex, surgical status, major presumptive clinical syndrome, SOFA score at time of randomisation and APACHE II score at ICU admission.		

TABLE 14 *Treatment effect in compliers*

Model	**Relative risk (95% CI) PAC vs control**
Unadjusted	1.04 (0.95 to 1.14)
Adjusted[a]	1.05 (0.94 to 1.15)
[a] Adjusted for non-compliance and contamination using the method of Cuzick and colleagues.[77]	

TABLE 15 *Subgroup analyses*

Subgroup	Hospital mortality		Adjusted hazard ratio (95% CI)	*p*-Value
	Control *n*/*N* (%)	PAC *n*/*N* (%)	PAC vs control	
Alternative cardiac output monitoring				0.48[c]
Stratum A (no option to use)	71/107 (66.4)	75/105 (71.4)	1.21 (0.87–1.68)	
Stratum B (option to use)	262/400 (65.5)	271/401 (67.6)	1.06 (0.90–1.26)	
APACHE II risk of death[a]				0.92[c]
0 to 0.281	89/158 (56.3)	101/169 (59.8)	1.14 (0.85–1.52)	
0.282 to 0.499	107/158 (67.7)	108/156 (69.2)	1.08 (0.83–1.42)	
0.500 to 1	123/167 (73.7)	124/154 (80.5)	1.09 (0.85–1.40)	
Major presumptive clinical syndrome				0.69[c]
Acute respiratory failure	38/66 (57.6)	48/68 (70.6)	1.39 (0.91–2.13)	
Multi-organ dysfunction	231/336 (68.8)	224/328 (68.3)	1.04 (0.87–1.26)	
Decompensated heart failure	35/56 (62.5)	39/55 (70.9)	1.07 (0.68–1.69)	
Other	29/49 (59.2)	35/55 (63.6)	1.13 (0.69–1.85)	
PACs per admission[b]				0.97[c]
<0.05	71/100 (71.0)	79/99 (79.8)	1.19 (0.85–1.65)	
0.05–0.11	62/100 (62.0)	60/96 (62.5)	1.11 (0.77–1.61)	
0.11–0.15	71/102 (69.6)	70/106 (66.0)	1.14 (0.81–1.60)	
≥0.15	56/90 (62.2)	63/88 (71.5)	1.25 (0.86–1.81)	

[a] Excludes 44 patients in the control group and 47 in the PAC group who stayed <8 h in the ICU or who had incomplete data.
[b] Based on 782 admissions from 48 units (that participated in the PAC-Man Study) in England and Wales with historic data on PAC use from the Audit Commission survey.[70]
[c] *p*-Value for test of interaction between treatment and subgroup in adjusted Cox proportional hazards model.

TABLE 16 *Secondary outcomes*

Outcome measure		Control	PAC	*p*-Value
ICU length of stay (days)				
Survivors	Median (IQR)	11.0 (5.7–21.0)	12.1 (6.2–22.3)	0.26[a]
	Mean	15.7	16.8	0.43[b]
Non-survivors	Median (IQR)	2.5 (0.8–7.2)	2.6 (0.7–8.4)	0.71[a]
	Mean	7.1	6.8	0.90[b]
Hospital length of stay (days)				
Survivors	Median (IQR)	40 (21–70)	34 (23–61)	0.43[a]
	Mean	52.4	48.9	0.51[b]
Non-survivors	Median (IQR)	3 (1–11)	3 (1–11)	0.90[a]
	Mean	12.4	10.9	0.49[b]
Organ-days of support in ICU				
Survivors	Median (IQR)	19 (10–32)	19 (12–33)	0.32[a]
	Mean	25.2	26.2	0.66[b]
Non-survivors	Median (IQR)	8 (4–21)	9 (4–20)	0.74[a]
	Mean	15.2	16.7	0.37[b]

[a] *p*-Value from Wilcoxon rank-sum test for difference in distribution.
[b] *p*-Value from bootstrap *t*-test for difference in mean.

Changes in management as a direct result of PAC insertion

One or more changes in clinical management within 2 hours of insertion of the PAC were reported in 389 (80.0%) of the PAC group patients (*Table 17*). The most frequently reported changes were infusion of 200 ml or more of fluid above maintenance levels in 1 hour (n = 205, 42.2%), change in the dose of a vasoactive drug of >25% (n = 211, 43.4%) and introduction of a vasoactive drug (n = 156, 32.1%).

TABLE 17 *Changes in management following PAC insertion (PAC group, n = 486)*

Change in management	*n* (%)
Change in dose of vasoactive or inotropic drug of more than 25%	211 (43.4)
Infusion of 200 ml or more of fluid above maintenance in 1 hour	205 (42.2)
Introduction of a vasoactive or inotropic drug	156 (32.1)
Additional diuretic therapy	36 (7.4)
Previously unscheduled haemofiltration/dialysis session	17 (3.5)
Previously unscheduled imaging (other than a chest X-ray)	5 (1.0)
Other change	14 (2.9)

TABLE 18 *Use of alternative cardiac output monitoring devices by treatment group*

Flow measurement technique	Control, *n* (%) (*n* = 508)	PAC, *n* (%) (*n* = 506)
Trans-oesophageal Doppler	179 (35.2)	55 (10.9)
Indicator dilution	124 (24.4)	15 (3.0)
Trans-thoracic Doppler	5 (1.0)	7 (1.4)
Trans-thoracic bioimpedance	2 (0.4)	5 (1.0)
Other flow measurement device	5 (1.0)	2 (0.4)

TABLE 19 *Use of alternative cardiac output monitoring devices by stratum*

Flow measurement technique	Stratum A (no option to use), *n* (%) (*n* = 212)	Stratum B (no option to use), *n* (%) (*n* = 802)
Trans-oesophageal Doppler	4 (1.9)	230 (28.7)
Indicator dilution	2 (0.9)	137 (17.1)
Trans-thoracic Doppler	1 (0.5)	11 (1.4)
Trans-thoracic bioimpedance	1 (0.5)	6 (0.8)
Other flow measurement device	0	7 (0.9)

The first PAC remained in place for a median duration of 1.96 days (interquartile range 1.0–3.0 days); the total number of days that a PAC was indwelling in individual patients was a median of 3 (interquartile range 2–4) days.

Use of alternative cardiac output monitoring devices

Table 18 details the use of alternative cardiac monitoring devices by treatment group. The devices most frequently used were the oesophageal Doppler and pulse contour/indicator dilution systems. The use of alternative devices by stratum is detailed in *Table 19*. There were five patients in stratum A who were managed with one or more alternative devices.

Meta-analysis

Data from the current RCT were combined with data from three previous trials of general intensive care patients identified in the systematic review[17,32,33] to give a pooled OR of 1.05 (95% CI 0.87 to 1.26) (*Figure 8*).

Discussion

In this trial, the largest academic-funded RCT performed to date in UK intensive care, no statistically significant difference in hospital mortality was found between critically ill patients managed with or without a PAC. Similarly, there was no statistically significant difference in length of stay in either intensive care or hospital or in organ-days of support between the two groups.

The pragmatic design of the PAC-Man Study reflected the lack of consensus within the critical care community on specific patient management protocols. Although some argued strongly for a structured approach (treatment algorithms based on haemodynamic variables), the lack of reliable data meant that no common strategy could be agreed regarding timing or indications for catheter insertion, selection and manipulation of specific drugs, fluids and support devices or haemodynamic end-points. Furthermore, the trial outcome would then have reflected the

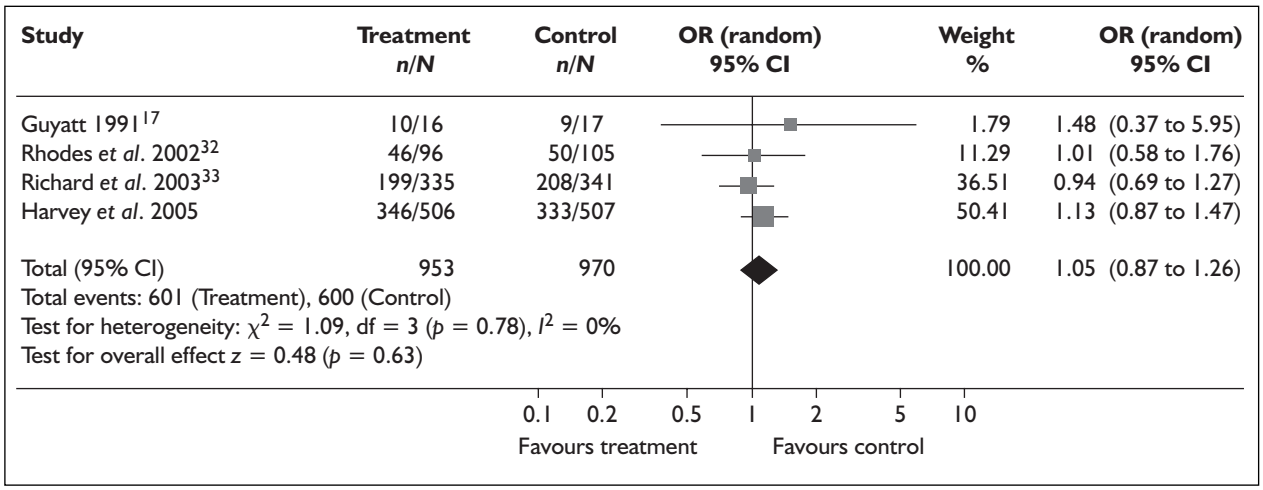


FIGURE 8 *Management with a PAC versus management without a PAC: studies of general ICU patients*

combination of choice of strategy employed and PAC use rather than the use of the PAC itself, which was the primary question demanded by the funding body, particularly in light of its potential to cause harm as suggested by Connors and colleagues' study[18] and a similar analysis in Scotland.[30] The RCT thus evaluated 'usual' management with a PAC and, as a result, reflected current practice in ICUs within the NHS.

Allowing the option to use alternative cardiac output monitoring technologies in some ICUs (stratum B) also reflected 'usual' or 'current' care within the NHS. Adoption of these technologies has markedly increased in recent years,[79] which was reflected by the large number of ICUs that opted to be in stratum B. Of these, 25% (n = 12) were university hospitals compared with 5.9% (n = 1) in stratum A. The small number of patients randomised into stratum A (n = 212) prevented a sufficiently powered comparison of management with a PAC against no cardiac output monitoring. Although there was no evidence of interaction between treatment effect and stratum, the statistical power of such tests is low and there is still a need for a formal evaluation of these less invasive monitoring devices in the critically ill.

To maximise the external validity of the trial, minimal patient exclusion criteria were employed to allow the enrolment of the majority of patients deemed to require management with a PAC. In addition, all general, adult ICUs in the UK were invited to participate in the trial, of which approximately one quarter ultimately took part, with a representative proportion of ICUs being located in university, university affiliated and non-university hospitals. External validity may also be threatened if potential trial participants are excluded because clinicians lack equipoise and do not invite them to participate, because of administrative errors, or because they decline to participate.[80] Of the 1263 patients who were identified as being eligible for the trial, 222 (17.6%) were excluded. Of these, nearly half (49.5%) were because the responsible treating clinician lacked equipoise. The patient's relatives refused permission in 47 cases (21.2%) and in another 23 cases (10.4%) administrative errors meant that the patient or their relatives were not invited to participate. Excluded patients were comparable to those included in the trial with regard to age and sex. However, it is not known whether they differed in other ways, such as severity of illness, as these data could not be collected. Documentation of eligible patients excluded from the trial was at the discretion of participating ICUs and may have been under-recorded. Regular contact was maintained with participating ICUs throughout the trial and maintenance of the screening log was emphasised each time. We are therefore reasonably confident that the estimate of excluded patients was accurate. Other similar trials have either not reported the number of patients excluded[33] or have reported much higher exclusion rates. For example, Guyatt[17] reported that of 148 eligible patients, 77.7% (n = 115) were excluded, most frequently because the attending physician felt that it was unethical not to use a PAC (n = 52). However, there was no difference in the severity of illness between eligible patients excluded compared with those included.[17] Sandham and colleagues[41] reported that 1994 patients (52.4%) of 3803 eligible patients were randomised into their perioperative study. The remaining 1809 patients were not enrolled because

they declined to participate (n = 1074), there was no ICU bed available (n = 370) or they were not invited to participate by the clinician (n = 365). The authors did not report whether there were important differences, such as severity of illness, between included and excluded patients.

To ensure high internal validity, a rigorous process of randomisation was adopted. Compliance with randomisation was high and complete follow-up of all patients was achieved. As a result, the two groups were comparable for all the important known prognostic factors.

The PAC-Man Study is the first RCT of this intervention with sufficient power (83%) to detect a 10% change in hospital mortality. Our results are similar to two smaller, pragmatic studies previously conducted in critically ill patients in intensive care. One was a single-centre study in the UK of 201 patients with predominantly septic or cardiogenic shock.[32] Mortality at 28 days was similar for patients managed with (47.9%) and without (47.6%) a PAC. The other study was a multi-centre RCT, conducted in 36 ICUs in France, of 676 patients with sepsis and/or acute respiratory distress syndrome.[33] The authors reported higher 28-day mortality, but again there was no difference between the two groups: 59.4 versus 61% in patients managed with and without a PAC, respectively.

Thus, since the publication of the non-randomised study by Connors and colleagues in 1996,[18] a large amount of evidence has now been accumulated from RCTs. The combined data from these trials refute the suggestion by Connors and colleagues[18] that PAC use is related to a significant increase in mortality, but suggest that no benefit accrues from use either.

The generalisability of our findings to other countries remains to be determined. The main indication for insertion of a PAC in our trial was to guide vasoactive drug treatment (>80% of patients), suggesting a similar patient cohort to that enrolled in the French multi-centre study. However, their use of the PAC in other patient groups such as heart failure was not stated.[33]

The high APACHE II scores and high hospital mortality seen in our trial population indicate that the most seriously ill patients were clearly being identified for management with a PAC. Reserving the use of the PAC primarily for these critically ill patients with a poor prognosis may reduce its effectiveness in improving outcome. This is supported by a meta-analysis[81] showing outcome benefit from the PAC when used to direct protocolised haemodynamic interventions in high-risk surgical patients, but not when commenced in critically ill intensive care patients with established multiple organ failure and a predicted high risk of death. This suggests that a different treatment paradigm other than manipulation of macrocirculatory variables may need to be considered in such patients.[82]

The lack of overall benefit in these studies of PAC use in general intensive care patients could be variously explained by statistical chance, by misinterpretation of PAC-derived data, by correct interpretation of data but formulation of ineffective treatment plans, by the whole paradigm by which we use haemodynamic data from PACs being incorrect or because there is no additional advantage being gained from a more detailed knowledge of haemodynamics however used. We undertook a large, well-powered trial to minimise the possibility of a beta (Type II) statistical error, and the confirmatory results from the meta-analysis make the possibility of a statistical error even more unlikely. We have no evidence to confirm or refute whether technical aspects of PAC use were undertaken correctly. We did not directly examine quality of use (data interpretation and treatment plan formulation), although no outcome difference was seen on comparing units with high and low historical frequency of use, which was used as a marker of experience. However, previous studies[10–12] have highlighted high levels of ignorance in terms of correct waveform recognition and data interpretation among both ICU doctors and nurses. Iberti and colleagues administered a 31-question multiple-choice examination to 496 physicians practising in 13 medical facilities in the USA and Canada,[10] and a 37-question multiple-choice examination to 216 nurses attending the American Association of Critical Care Nurses' National Teaching Institute conference.[11] In both studies they found wide variations in the understanding of the use of the PAC. The mean test score for the physicians was 20.7 (67% correct) with an SD of 5.4 and a range of 6–31 (19–100%). Mean scores varied independently by training, frequency of use of PAC data in treatment of patients, frequency of inserting a PAC and whether the respondent's hospital was a primary medical school affiliate. The mean test score for the nurses was 16.5 (48.5% correct) with an SD of 5.7 and a range of 1–31. Test scores were significantly associated with years of experience in critical care, critical care registered nurse certification, responsibility for repositioning and manipulating the PAC, frequency of use and self-assessed

adequacy of knowledge. Gnaegi and colleagues[12] used the same tool to investigate French, Swiss and Belgian intensive care clinicians' knowledge and reported similar results. Hence it is possible that the data derived from the PACs were used incorrectly. It would be unwise, however, to attribute failure of the trial to show benefit to incorrect PAC use without further data, particularly as clinicians cannot agree on what is 'correct use'. A large proportion of patients did have some treatment modification after the PAC was placed, suggesting that treatment plans were formulated based on the data obtained from the PAC. However, these changes did not translate to an outcome advantage. Hence the treatment plans were either incorrect or ineffective. Assuming that the plans were correct according to the current paradigm, this may suggest that the whole basis on which we manage macrocirculatory disturbances may be of no benefit to the patient. No deaths were directly attributed to PAC insertion in our trial, although 9.5% of patients did suffer significant insertion-related complications. We did not study late-onset complications such as infection.

In conclusion, this multi-centre RCT has demonstrated that the current use of PACs in UK clinical practice does not reduce hospital mortality in general, adult ICU patients. However, the PAC is essentially a measuring/monitoring device, providing very comprehensive data on circulatory variables. If knowledge of these variables does not influence outcome, other devices that measure the same variables using different technologies may not produce any benefit to the patient either. These technologies therefore should come under closer scrutiny.

Chapter 4

Economic evaluation of the incremental cost-effectiveness of withdrawing pulmonary artery catheters from routine use in intensive care

Introduction

One of the limitations of the existing evidence on PACs, from the perspective of healthcare decision-makers, is that none of the trials of PAC use in general intensive care patients previously incorporated an economic evaluation. The only economic evaluation of PAC use comes from a retrospective, case-controlled study by Connors and colleagues, which found an increase in resource use associated with the use of PACs and increased odds of 30-day mortality.[18] The limitations of this study were discussed at length in the literature following its publication, and it is now generally held that this study does not provide a sound foundation for healthcare decision-making.[3,5,25,26]

This pre-existing evidence does provide some information on outcomes, but this has only been subject to hypothesis testing. Effectively, doctors have decided that the available evidence is insufficient to support a decision to withdraw the PAC and are awaiting further information.

The objective of the economic evaluation was to identify any difference in the expected costs and outcomes of patients treated with and without a PAC in order to inform healthcare decision-making processes, from the perspective of the NHS. As the use of a PAC is an established intervention, 'No PAC' is characterised as the new intervention for the purposes of the economic evaluation. The analysis therefore gives the implications of implementing a new treatment in place of standard treatment, which is the relevant question for the decision-maker, that is, whether we should provide critical care without using the PAC.

Classical inference analysis assesses whether the data are consistent with rejecting the null hypothesis of difference in costs or outcomes, using the standard error probabilities. By contrast, the economic evaluation addresses the question that the health service needs to answer, 'What would be the impact on costs and outcomes if the PAC was withdrawn from use in the NHS?' Without an answer to this question, the NHS does not have a relevant evidence basis for its decision regarding the future use of the PAC.

Methods

Form of economic evaluation

The primary economic evaluation is a cost–utility analysis (CUA), reporting the cost per quality-adjusted life-year (QALY) gained from not using the PAC. The secondary analysis is a cost-effectiveness analysis (CEA), and reports the cost per life gained from not using the PAC.

These two forms of economic evaluation differ in terms of the outcome measure that they use. CEA can be performed on any alternatives which have a common effect, and the result is expressed as the cost per unit of effect. CUA employs utility as a measure of the value of a programme and the most common measure used for this is the QALY. Results are expressed as the cost per QALY.[83]

CUA is increasingly required by decision-makers both in the UK and elsewhere, as it allows the comparison of interventions across all areas of health care.[84,85] Hence, the analysis allows the reader to compare the cost-effectiveness of withdrawing PAC with other interventions and to consider the likely attitude of healthcare decision-making bodies, such as the National Institute for Health and Clinical Excellence (NICE),[85] to the results.

Outcomes

The primary outcome of the economic evaluation was QALYs. We estimated the quality-adjusted life expectancy for each survivor at hospital discharge based upon the Office of National Statistics age- and sex-specific life expectancy tables[86] and the EQ-5D age- and sex-specific quality of life weights.[87] This was calculated as the sum of the EQ-5D utility value for each year of life remaining. It is well established that mortality

after hospital discharge is higher in patients who have survived a period of intensive care than in the general population.[88] Although there are reports of variations in both the timing and absolute value of this mortality by some diagnostic groups, the data necessary to estimate survival in the heterogeneous PAC-Man RCT population and incorporate them into our analyses were not available,[88] so population estimates were used.

Costs

The perspective for the economic evaluation was the NHS, hence only costs incurred by the NHS were considered. Although other costs certainly fall on the patients and their families, and possibly social services, it is likely that these will be small in relation to the NHS costs and unlikely to affect the results of the analysis.

For each patient, the length of stay in the original recruiting ICU and the total length of stay in an acute hospital were recorded. Routine NHS data sources were used to obtain unit costs. The NHS reference costs for a day of intensive care and for a day of medical ward care were obtained from the NHS reference cost database 2002–3.[89] No distinction was made between patients cared for on a medical or surgical ward during a portion of their stay; they were all regarded as 'medical' patients. Cost data were obtained from ICUs in the trial and used to validate the NHS reference cost, as an estimate of the mean cost per day of care in an ICU.

All ICUs participating in the trial were asked to submit data on the costs of their ICU for the financial year 2002–3 via a series of four cost questionnaires (Appendix 14). The results of these were used to calculate a total cost per ICU and this was divided by the total days of care provided by that ICU during the same period, to give an estimate of the average cost per day.

The cost of each patient's intensive care episode was calculated as the number of days of intensive care multiplied by the mean cost of a day of intensive care reported in the NHS reference cost database. The cost of each patient's hospital stay outside the ICU was estimated as the mean cost of a day on a medical ward, multiplied by the number of days on the ward recorded in the case report form. The total cost for each patient was the sum of these two figures.

Future healthcare costs

Consistent with current practice, future unrelated healthcare costs were not incorporated into the economic evaluation.[90] In the absence of data to the contrary, we had to assume that future related costs were negligible. We believe that this is a reasonable approach as it would be difficult to establish that healthcare usage after discharge from hospital was attributable to the use or absence of a PAC, rather than the primary reason for admission.

Discounting

As all events within the trial occurred within a single year, there was no need to discount costs or outcomes for the CEA. For the CUA, future QALYs were discounted at 3.5% per annum, as per the recommendations of the UK Treasury Green Book[91] and the current guidance from NICE.[85]

Sensitivity analysis

Mean costs and outcomes were calculated from the trial data and provide sample estimates of the parameters of interest to decision-makers, the population mean costs and outcomes. It is now good practice to address explicitly the uncertainty regarding the true population values of these parameters.[90] It is increasingly recognised that although one-way sensitivity analyses can provide some insight into the potential importance of this uncertainty, probabilistic sensitivity analysis is the most appropriate method of incorporating the uncertainty across all the parameters into the results of an economic evaluation.[85]

We used the non-parametric bootstrap to construct probability distributions for the population mean costs and outcomes for patients managed with and without a PAC.[92]

Incremental costs and outcomes were calculated for each bootstrapped simulation and plotted on the incremental cost effectiveness plane. This was repeated 10,000 times.[93] The 10,000 simulations are used to construct a cost-effectiveness acceptability curve.[94]

We report the expected cost per QALY and expected cost per life gained from the probabilistic sensitivity analysis.

Results

Table 20 reports the descriptive statistics for the ICU, ward and total costs for the patients in each arm of the trial, calculated using the NHS reference costs. The average cost of a day in intensive care using 2002–3 reference costs was £1293 and the average cost from data we collected

TABLE 20 *Descriptive statistics for ward, ICU and total cost (£) by group*

	Mean	Maximum	Minimum	SEM
Ward cost				
No PAC	4,108	115,216	0[a]	430
PAC	3,393	66,158	0[a]	330
Intensive care cost				
No PAC	15,103	474,591	1,293	1,146
PAC	15,219	305,186	1,293	921
Total cost per patient				
No PAC	19,211	474,591	1,293	1,290
PAC	18,612	305,186	1,293	1,056

[a] The minimum ward cost of £0 reflects a number of patients who were admitted directly to ICU but did not survive.

TABLE 21 *Patient outcomes by allocated group*

	Mortality	QALYs (SEM)
No PAC	0.66	3.95 (0.27)
PAC	0.68	3.75 (0.28)

from the trial ICUs (n = 33) for the same financial year was £1353. The mean total cost per patient is £18,612 in the PAC group compared with £19,210 in the No PAC group.

Table 21 reports the outcomes for each group for QALYs and mortality. In the PAC group, the mean QALY value was 3.75, compared with 3.95 in the No PAC group.

Figure 9 presents the scatter plots on the cost-effectiveness plane for the cost per QALY gained and the cost per life gained from the withdrawal of the PAC, using the non-parametric bootstrap procedure. In both cases it can be seen that the majority of simulations lie in the north-east quadrant of the plane, which means an increase in cost and increase in effect, indicating that the withdrawal of the PAC is most likely to produce a health gain, but with an increase in cost.

The bootstrap analysis produced an expected cost per QALY gained from the withdrawal of the PAC of £2985. The associated expected cost per life gained from the withdrawal of the PAC was £22,038.

Figures 10 and *11* are derived from the same data as *Figure 9*, but they report the probability that the withdrawal of the PAC from the NHS will be cost-effective over a range of cost-effectiveness thresholds. *Figure 10* is the CEAC for QALYs and *Figure 11* is the CEAC for hospital mortality.

It is worth noting that there is no cost-effectiveness threshold at which the probability that withdrawal of the PAC is cost-effective equals one. Hence, there is some risk that the withdrawal of the PAC will do harm. However, this risk would only disappear if we had perfect information, which is never the case in practice.

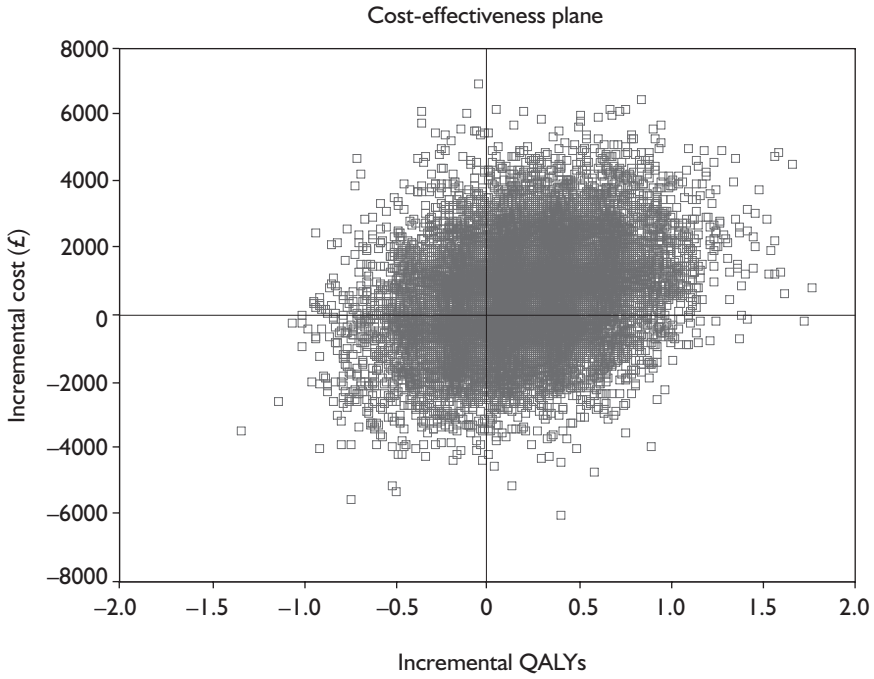
Discussion

RCTs to date have concluded that there is no significant difference in clinical outcomes between patients managed with and without a PAC in intensive care. However, such research has characterised the uncertainty using an arbitrary threshold, above which uncertainty is deemed to be 'significant' i.e. it should influence decisions, and below which it is deemed 'non-significant' and therefore should not influence decisions. It has also almost completely ignored questions relating to the cost-effectiveness of PACs.

Here, we have examined the cost-effectiveness of PAC use in managing critically ill patients from a decision science perspective. Our analysis, based on the data collected during this high-quality RCT, indicates that withdrawing PACs from routine use in the NHS is likely to produce health gains, at a price which is considered acceptable by current decision-making bodies.[85] The expected estimate of the cost per QALY gained from withdrawing the PAC is £2985, which compares favourably with many routinely provided therapies, such as statins for the management of coronary heart disease.[95]

The cost-effectiveness of withdrawing the PAC is driven by both the costs and the outcomes. Our best estimate of the risk of death (the mean) is higher in the PAC group, that is, PAC has a

Incremental cost and QALYs



Incremental cost and lives saved

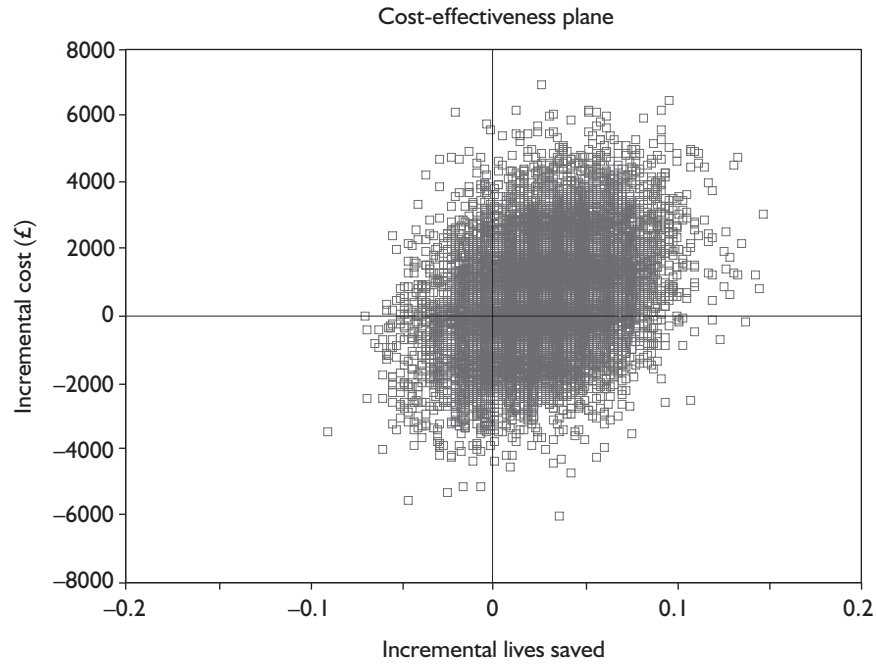


FIGURE 9 *Bootstrap plots*

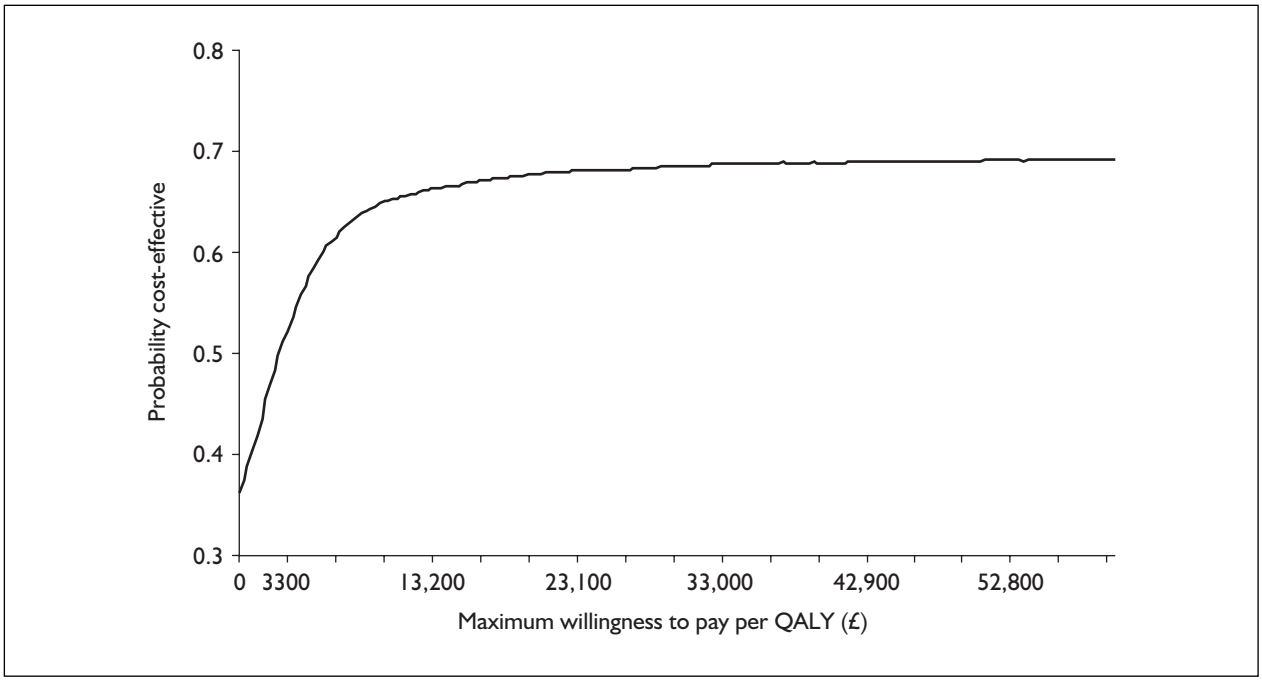


FIGURE 10 *Cost-effectiveness acceptability curve: cost per QALY*

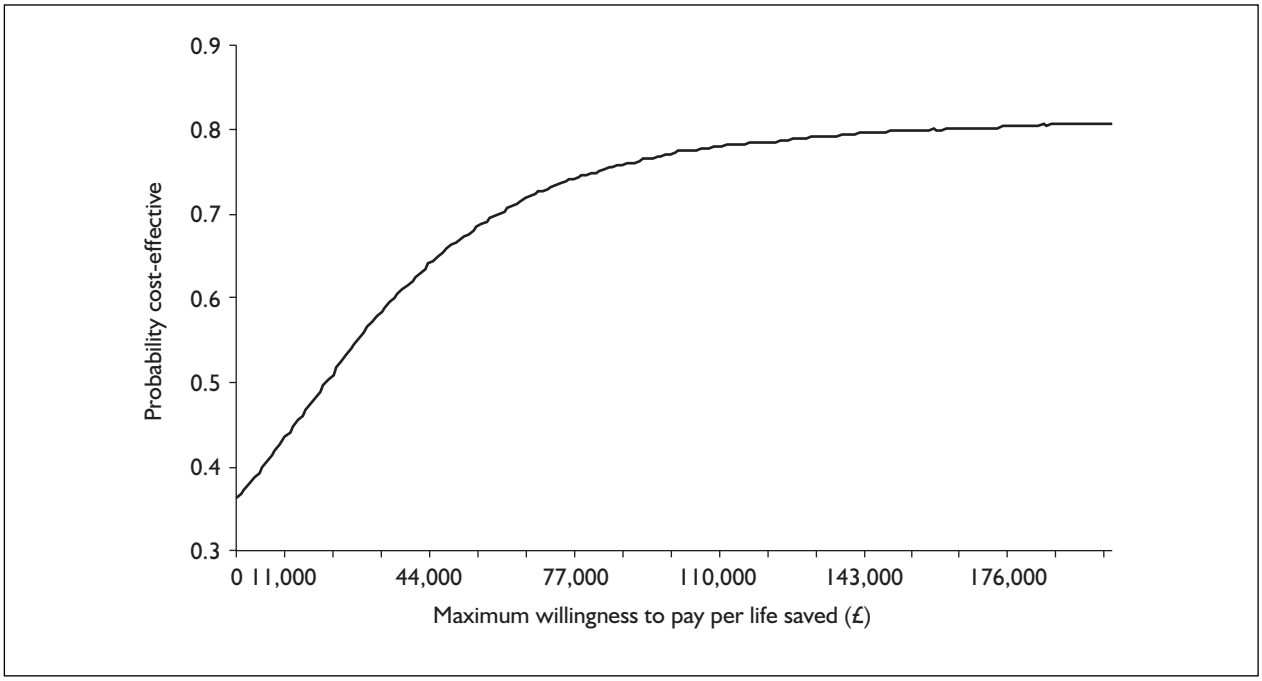


FIGURE 11 *Cost-effectiveness acceptability curve: cost per life gained*

negative impact on health. At the same time, the PAC is associated with a shorter length of hospital stay. This is potentially explained by the increased mortality. The combined effect is that we would expect withdrawal of the PAC to increase total costs and increase total health gain.

There are a number of limitations to this analysis. We have assumed general population life expectancy after hospital discharge. Although there is some evidence of excess mortality in survivors of intensive care[88] from a single-centre retrospective study, this does not provide sufficient

information to adjust the patient-level life expectancy predictions. Also, our analysis examines the difference in survival between two ICU populations which are likely to be equally affected and, therefore, the impact of the excess general mortality post-ICU is likely to be small. Similarly, it would be desirable to use health-related quality of life data from intensive care survivors. We failed to identify an appropriate dataset. However, given that the focus of the analysis is on the difference between two ICU populations, it is likely that the impact of this failure upon our results would be small.

A number of factors may lead to an underestimate of the uncertainty around the cost-effectiveness ratio. These are the use of general population life expectancy, the use of the age- and sex-adjusted EQ-5D utility values and the use of a fixed cost per day for the costs, as there will be variations in other resource use not fully captured by length of stay. However, there is no reason to believe that they may impact on the expectation of the cost-effectiveness, which is the important figure for the decision.

Within the decision analysis framework, the decision criterion is that the expected cost per life saved/QALY is at or below the societal willingness to pay for the unit of health gain. However, a cost-effectiveness analysis will rarely, if ever, completely describe the decision problem. Decision-makers are often interested in the degree of uncertainty around the cost-effectiveness estimates.[85] In this context, it is worth noting that mortality analysis indicates a 19% risk of harm against an 81% chance of benefit even when the willingness to pay equals £200,000 per life saved, that is, the odds are 4:1 in favour of the withdrawal of the PAC leading to health gain. To conclude that there is no difference between management with a PAC and management without a PAC would in effect be a decision to support the continued option to use the PAC as per current clinical practice.

An important issue for decision-makers to consider when choosing to withdraw funding for an established technology or not to fund a new technology is whether the decision is irreversible, that is, if further evidence were to demonstrate that PACs were in fact a cost-effective intervention, would it be possible to reintroduce them to the NHS. Palmer and Smith proposed that real option pricing could be used to incorporate the value of future opportunities foregone by making an irreversible decision.[96] However, as PACs are still in widespread use in other countries, and are used in the NHS outside critical care, it is unlikely that the decision to withdraw PAC from use in UK critical care medicine would be irreversible.[97]

Potentially more important than the specific result of this trial is the demonstration of the difference in the implications of the PAC-Man Study when the data are analysed to inform decision-making, rather than test a hypothesis. The 5% significance level is a well-established convention. It adopts a conservative approach to rejecting the null hypothesis. However, hypotheses are not decisions. Decisions directly affect the cost and outcomes of healthcare. It seems reasonable that decisions should be based upon our expectation of what will happen rather than whether a hypothesis has been proven subject to an arbitrary level of significance. Therefore, trials which report no statistically significant difference should not be interpreted as evidence that the expected outcomes of comparators are equivalent.

In many areas of research, particularly laboratory research and some clinical trials, hypothesis testing is the appropriate framework. However, whenever trials are intended to inform decisions regarding clinical practice and resource allocation, decision analysis is the appropriate framework. Any other approach makes extremely inefficient use of the evidence generated by the trial and risks making unsupported conclusions. The implication of this is that Phase III trials and pragmatic trials should be analysed in a decision analytic framework to inform decision-making, even if a conventional hypothesis testing analysis is also performed for licensing purposes.

This issue has been well rehearsed in the health economics literature[94,98] and was highlighted in an editorial in *The Lancet*.[99] The most recent methods guidance from NICE for England and Wales strongly promotes the decision analysis approach to the analysis of both effectiveness and cost-effectiveness of therapies.[85] There is also some evidence that the Federal Drug Administration in the USA is interested in non-frequentist methods, to make the maximum use of available data.[100]

A strength of this approach is that it gives complete information on uncertainty surrounding the information given. Thus, where differences are generated from small amounts of data, they will correspondingly have large uncertainty. Similarly, when the amount of data is larger, the uncertainty is lower. This avoids reliance on arbitrary thresholds such as those used in conventional frequentist analysis.

Chapter 5

Overall conclusions

Where now for the PAC? All large RCTs to date assessing its effectiveness in intensive care have found no overall advantage, and the addition of this study's results to the meta-analysis reinforces this view. The increasing availability of sophisticated and less invasive diagnostic technologies such as the trans-oesophageal Doppler measurement may lead to these devices gradually replacing the PAC in clinical use. Whether these devices can produce a survival advantage for patients when PACs cannot remains unclear, although as they provide essentially the same information as PACs it seems likely that they will be equally ineffective. If the PAC is to be retained in clinical practice, its declining use[101] and hence decreased familiarity across all strata of medical and nursing staff mandates regular training to maintain these skills during both day and night, incurring costs that are difficult to justify, especially as the cost-effectiveness analysis suggests that withdrawing the PAC from routine use in the NHS is likely to produce health gains.

Chapter 6

Recommendations for future research

The PAC is still regarded as the gold standard method for measuring cardiac output in a critical care setting, but whether this will still be the case in the future remains uncertain, given the decline in use in recent years.[101] Part of this decline is related to the increased use of less- or non-invasive cardiac output monitoring devices. Although these devices use different technologies and provide different sets of additional primary and derived haemodynamic variables, essentially they are all used to monitor haemodynamics. The problem is that we do not know whether the information that such devices deliver is of benefit to patients in terms of survival or other patient-centred advantages. The fact that the PAC, the most data-rich haemodynamic monitoring device, does not alter patient outcome suggests that close scrutiny of these devices as a whole is warranted Therefore, the first area for research is to conduct studies to investigate whether monitoring cardiac output, using any of the available devices, improves patient outcome.

The second area for research is to determine optimal management protocols for circulatory pressures, oxygen delivery, fluid and inotrope therapy using targeted end-points and to investigate the benefits of early goal-directed therapy in a multi-centre trial.

The third area for research is to conduct efficacy trials to examine the use of the PAC in specific patient groups using well-defined treatment protocols. This process has already started; the Fluid and Catheter Treatment Trial (FACTT) is using a 2×2 factorial study design to separate the effect of the PAC itself and the treatment algorithm by comparing the use of a liberal fluid management strategy with a conservative fluid management strategy, and comparing the use of a PAC with the use of a CVP catheter in patients with acute lung injury and acute respiratory distress syndrome. At the time of writing, this multi-centre RCT was ongoing in the USA, and aimed to enrol 1000 patients (250 patients in each of the four groups). Another multi-centre RCT, recently completed in the USA, is the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterisation Effectiveness (ESCAPE), which investigated the utility of the PAC in patients with advanced cardiac failure.[102] At the time of writing, the full trial report had not been published, although the results were presented at the American Heart Association's Scientific Sessions 2004, where it was reported that there was no difference in the number of deaths or in the number days spent in hospital for patients managed with a PAC compared with those managed without.[103] More studies are needed and perhaps the most obvious study follows on from the meta-analysis[81] showing that there may be a benefit from presurgical treatment of high-risk surgical patients with a PAC. Although appropriately designed studies in this area are vital, given the short supply of ICU beds in the NHS, the costs and logistics of undertaking such studies may be prohibitive.

As with PACs, efficacy studies of the new cardiac output monitoring devices in well-defined patient groups with clear treatment plans are urgently needed to prevent the same situation that has occurred with the PAC of widespread use and acceptance in the absence of data on effectiveness. Multiple single-centre perioperative studies using alternative cardiac output monitoring devices have shown outcome benefit when the devices were used to optimise fluid administration or target elevated levels of oxygen delivery either during or immediately after cardiac surgery,[104–106] orthopaedic surgery[107,108] or other high-risk surgery.[109] The fourth area of research is to conduct similar multi-centre studies in the critical care environment.

Two broader research issues arise from this study. The first is how to reconcile two different results from the same study. Using conventional hypothesis testing, the PAC-Man Study shows no benefit if PACs are used in general intensive care patients, but from a decision analysis perspective, it shows a probable small survival benefit if PACs are not used, and a cost per QALY that is in essence the cost of completion of care for these additional survivors. The hypothesis-testing approach was the basis on which the RCT was designed and powered and is the standard approach in academic medicine. The decision analytic approach of the cost-effectiveness evaluation seeks to find the 'best answer' from the

available data. The debate on how these approaches should be used to advise clinicians and healthcare commissioners is ongoing.

The second issue relates to the evaluation of critical care technologies, and especially monitoring technologies. Monitoring devices in use are often the result of incremental advances in technology, rather than totally novel techniques. For example, pulse-contour devices use a combination of an old technique (pulse contour analysis) combined with variants of other older techniques to allow them to be calibrated (indicator dilution cardiac output), which are all enabled by advances in transducer and microprocessor technology. The devices are usually approved by regulatory authorities as they perform the same core functions as predicate devices. There is rarely a situation where the technology is stable long enough to undertake an RCT. Even if clinical trials are undertaken, monitoring devices only provide data, and the patient's outcome depends on the actions resulting from interpretation of these data. Further work needs to be undertaken on how to evaluate not only monitoring technologies, but also the human factors that influence their effectiveness.

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Sheila Harvey (Research Fellow, ICNARC) conducted and analysed data for the systematic review, conducted the analysis and interpretation of data for the RCT and drafted the manuscript. Katherine Stevens (Research Associate in Health Economics) conducted the analysis and interpretation of data for the economic evaluation and drafted the manuscript. David Harrison (Statistician, ICNARC) conducted the analysis and interpretation of data for the RCT and drafted the manuscript. Duncan Young (Consultant Anaesthetist) conducted and analysed the data for the systematic review, interpreted the data for the RCT and assisted with drafting the manuscript. William Brampton (Consultant Anaesthetist) conducted the systematic review, interpreted the data for the RCT and assisted with drafting the manuscript. Chris McCabe (Senior Lecturer in Health Economics) designed the economic evaluation, analysed and interpreted the data and

drafted the manuscript. Mervyn Singer (Professor of Critical Care Medicine) conceived and designed the study, interpreted the data and drafted the manuscript. Kathy Rowan (Director, ICNARC) conceived and designed the study, conducted the systematic review, interpreted the data for the RCT and drafted the manuscript.

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Appendix 1

Cardiovascular and cardiac output monitoring devices

The pulmonary artery catheter (PAC)

The PAC is a multi-lumen plastic catheter between 80 and 100 cm long. It has one lumen opening at the tip of the catheter, one lumen leading to a small balloon just back from the tip of the catheter and one lumen leading to an opening on the side of the catheter about 30 cm from the tip. Most PACs have a thermistor (temperature sensor) fitted near the catheter tip.

The PAC is usually inserted, via an introducer device, into the subclavian vein or the internal jugular vein. Once the tip of the catheter is in the vein, the balloon is inflated with 1.5 ml of air. This increases the cross-sectional area at the tip of the catheter, and creates drag in the blood flowing in the vein. The catheter is then slowly advanced and the drag on the balloon guides the catheter tip into the superior vena cava, through the right atrium and right ventricle of the heart and into the pulmonary artery. The PAC continues to be advanced until it finally 'wedges' in a branch of the pulmonary artery, occluding the blood flow with the balloon. The pulmonary vasculature downstream from the occlusion acts as a conduit and transmits the atrial pressure in the left side of the heart to the catheter tip. The balloon is then deflated, and only inflated briefly to record the 'wedge' (left atrial) pressure.

The PAC lumens are connected to pressure transducers, which display waveforms on a monitor. The morphology of the waveforms and the absolute pressure recorded are used to confirm correct placement. Using the lumen leaving the side of the PAC, the atrial pressure in the right side of the heart can be recorded. By inflating the balloon, the atrial pressure in the left side of the heart can be recorded from the tip of the catheter. With the balloon deflated, the catheter tip lumen measures pulmonary artery pressure. Most PACs can also be used to determine cardiac output (strictly pulmonary blood flow) using a thermodilution technique. Most commonly this is an intermittent method whereby cold saline, at a known temperature below body temperature, is injected into the right atrial lumen and mixes with the blood due to turbulence in the right ventricle of the heart and the pulmonary outflow tract. The resultant fall in blood temperature is detected by the thermistor at the tip of the catheter and is a function of the flow of blood out of the right ventricle of the heart, that is, cardiac output. The higher the blood flow, the less temperature reduction is detected. If the blood pressure and heart rate are recorded simultaneously, a comprehensive set of primary and calculated variables can be generated to describe the functioning of the cardiovascular system. The left and right atrial pressures give an indication of 'preload', the pressure distending the ventricles and which partially determines cardiac output. The pulmonary artery and blood pressures are measures of 'afterload', the resistance to blood outflow from the ventricles. Dividing cardiac output by heart rate gives the stroke volume, a reasonably sensitive indicator of cardiac performance. It is also possible to calculate the hydraulic resistances of the systemic and pulmonary circulation and the work performed by each chamber of the heart per beat or per minute. If blood is sampled from the tip of the PAC in the pulmonary artery and from the arterial system (usually via a peripheral arterial cannula), the total oxygen consumption per minute can be calculated, along with the total oxygen delivery to the tissues per minute. Blood sampled variously from the right atrium, the 'wedged' catheter tip or the pulmonary artery can be used to diagnose various embolic diseases and intra-cardiac shunts (ventricular septal defects). Finally, the left and right atrial waveforms give some indication of tricuspid and mitral valve dysfunction.

The main risks of pulmonary artery catheterisation are damage or perforation to vessels during insertion, cardiac perforation, dysrhythmias, rupture of a branch of the pulmonary artery, pulmonary infarction, valve damage and endocarditis. These are all very rare with the exception of benign dysrhythmias.

PACs are most commonly used to determine the left ventricular preload (left atrial pressure) and cardiac output in patients presumed to have poor cardiac function. The measurements taken are then used to decide on the most appropriate treatment with fluids or inotropes to 'optimise' cardiac function. Less commonly, PACs are used to diagnose specific cardiac or pulmonary conditions. PAC use in the UK is almost wholly confined to ICUs, operating theatres and some cardiac catheter laboratories. Many variants on the 'standard' PAC have been developed, including devices to monitor continuous cardiac output and continuous mixed venous oxygen saturation, which, when compared with arterial oxygen saturation, will reflect changes in both cardiac output and the whole body oxygen consumption. Other variants include devices that can pace the heart, devices that can measure right ventricular ejection fraction (percentage of blood ejected from the heart with each beat) and devices with extra lumens for drug infusion.

Other cardiovascular/cardiac output monitoring devices

Echocardiography

This produces an ultrasound image of the heart, either in a normal two-dimensional view or a one linear dimensional/time format (M-mode). The standard echocardiogram is also known as a transthoracic echocardiogram as images of the cardiovascular system are taken through the chest wall. It allows assessment of cardiac valve function, the motion and morphology of the cardiac chambers and any abnormal communications between the left and right sides of the heart and can be used to calculate the cardiac output and left ventricular ejection fraction. In artificially ventilated patients, views are frequently severely limited owing to encroachment of the lungs into the acoustic window and the poor transmission of ultrasound through air. Echocardiography can also be undertaken using a trans-oesophageal probe with a pair of ultrasound transducers mounted on a modified gastroscope introduced into the oesophagus. Since the transducer is closer to the heart image, quality is improved and the lungs do not encroach. Some structures such as the aorta, pulmonary artery, heart valves and left and right atria are better imaged using trans-oesophageal echocardiography. However, although the procedure can be performed easily, conscious patients may require light sedation and a local anaesthetic lubricant for the pharynx. Echocardiography is essentially an intermittent diagnostic rather than monitoring technique.

Central venous pressure (CVP) catheter

This is a device that is introduced into the superior vena cava usually via one the large veins in the neck or chest and measures pressures in the superior vena cava or right atrium using a water manometer or an electronic transducer attached to a monitor. The superior vena cava pressure equates to the right atrial pressure and, in normal circumstances, right atrial pressure is an estimate of the volume of blood in the circulation (cardiac preload). As circulating blood volume is one of the determinants of cardiac output, manipulating the CVP using intravenous fluids and vasodilator drugs allows the cardiac output to be 'optimised'. However, right-sided heart pressures do not always equate with left-sided pressures, especially in the critically ill. Therefore, the CVP may not provide a reliable index of left-ventricular preload, which is the main determinant of cardiac output. For this reason, CVP is considered a less than optimal monitor of the circulation.

Trans-oesophageal Doppler measurement

Trans-oesophageal Doppler measurement of cardiac output uses an ultrasound probe that is placed in the mid-oesophagus via the nose or mouth and directed at the descending aorta. As the oesophagus and aorta are adjacent and parallel in the mid-chest, the geometric relationship between the aorta and the probe in the aorta is known. As a result, it is possible to measure the peak blood flow velocity in the descending aorta by using the Doppler shift in the frequency of ultrasound reflected from the blood cells, using a transducer at the tip of the flexible probe. The amount of blood ejected with each heart beat (stroke volume) is obtained by multiplying mean stroke distance (aortic blood flow velocity–time integral) by the aortic cross-sectional area to give blood flow volume per heart beat in the visualised area. Cardiac output is then calculated by multiplying the stroke volume by heart rate. The aortic cross-sectional area can be measured either at the bedside using trans-oesophageal echocardiography or derived from a nomogram based on the patient's age, weight and height. Some oesophageal Doppler devices have an M-mode ultrasound transducer incorporated into their probe in order to measure aortic diameter instantaneously, but viewing angle is critical for this to be correct. Assumptions are made about the relationship between the peak flow and the mean blood flow velocity to give stroke distance. The device does not provide any information about pressures in the cardiac

chambers, although some information can be obtained on cardiac contractility and vascular resistance from the velocity–time waveform. The device actually measures descending aortic blood flow, not true cardiac output, though these are usually linked in a fixed ratio.

Although the probe is small, it is not well tolerated by conscious patients and its use is confined to sedated or anaesthetised patients. The advantages are that it is a simple technique and it is fairly easy to achieve adequate probe positioning. The main complication is trauma to the pharynx and oesophagus.

Trans-thoracic Doppler measurement

Trans-thoracic Doppler measurement is similar to trans-oesophageal Doppler cardiac output measurement. The ultrasound probe is placed externally on the sternal notch (the depression at the top of the sternum) and ascending aortic blood flow is determined from the product of blood velocity and aortic cross-sectional area. The device is less invasive than the trans-oesophageal Doppler probe, which means that it can be used in conscious patients. However, it can be difficult to maintain a constant angle between the ascending aorta and the probe, so it is often difficult to obtain reliable measurements. The device does not provide any information about pressures in the cardiac chambers or the great veins, although, as with trans-oesophageal Doppler measurement, some information can be obtained on cardiac contractility and vascular resistance from the velocity–time waveform.

Impedance cardiography

This is a non-invasive method that monitors the cardiac output continuously without the need for a high degree of operator skill. The measurement of cardiac output is based on the principle that changes in trans-thoracic impedance occur when blood is ejected from the left ventricle. This effect is used to determine stroke volume from equations utilising the electrical field size of the thorax, base thoracic impedance, fluctuation related to systole and ventricular ejection time. A correction factor for sex, height and weight is also introduced. The technique utilises four pairs of electrodes placed in proscribed positions on the neck and thorax connected to a monitor which measures trans-thoracic impedance using a low-amplitude, high-frequency current applied across the electrodes. Some indirect inferences about cardiac performance can be made from the impedance–time waveform. It is of limited value in the critically ill who often have very low baseline thoracic impedances due to increased lung water. The device does not measure vascular pressures.

Pulse contour methods

These analyse arterial pulse waveforms for calculation of cardiac output. Pulse waveforms are derived from a large peripheral artery such as the axillary or femoral artery. The notion that stroke volume can be quantified from the pulse pressure assumes that the rate of blood flow from the arterial to the venous system is proportional to the rate of arterial pressure decline. Trans-pulmonary thermal indicator dilution is used initially and at regular intervals to measure cardiac output in order to calibrate the software. The calibration involves injecting cold saline solution into a central vein and measuring the temperature change using a thermistor on the tip the arterial cannula. The advantage of this technique is that it provides continuous measurement of cardiac output and is suitable for both conscious and unconscious patients. However, it is only accurate in patients in sinus rhythm. Arterial and central venous pressures are also recorded, so a number of calculated haemodynamic variables can be obtained.

A similar technique (indicator dilution method) involves using dilute lithium chloride solution as the indicator for calibration, with a fast-responding lithium ion-selective electrode as the sensor on the arterial side of the circulation, and then uses pulse contour analysis for monitoring cardiac output.

Techniques to measure cardiac output using variants of the Fick principle

These rely on the uptake of an indicator gas from the lungs. If the amount of gas taken up in unit time is known, and the solubility of the gas on blood is known, pulmonary blood flow can be calculated. Although acetylene, nitrous oxide and oxygen have been used in the past, the only commercially available device uses carbon dioxide. A small ‘dead space’ is introduced into the breathing circuit of an artificially ventilated patient, causing carbon dioxide to be inhaled. The cardiac output is then determined from the subsequent change in end-tidal carbon dioxide concentration. The device is automated and makes regular measurements. This device does not measure vascular pressures.

Appendix 2

Search strategy for the systematic review

The search strategy and terms were as follows:

1 ((randomized controlled trial) or (controlled clinical trial) or (clinical trial)) in PT
2 placebo*
3 random*
4 control*
5 prospectiv*
6 volunteer*
7 clini*
8 trial*
9 (placebo* or random* or control* or prospectiv* or volunteer* or (clini* near trial*)) in TI,AB
10 "random-allocation"
11 "double-blind-method"
12 "single-blind-method"
13 "random-allocation" or "double-blind-method" or "single-blind-method"
14 "randomized-controlled-trials"/all subheadings
15 "follow-up-studies"/all subheadings
16 "prospective-studies"/all subheadings
17 explode "clinical-trials"/all subheadings
18 explode "evaluation-studies"/all subheadings
19 "placebos"/all subheadings
20 TG=comparative-study
21 "research-design"/all subheadings
22 singl*
23 doubl*
24 tripl*
25 trebl*
26 blind*
27 mask*
28 (singl* or doubl* or tripl* or trebl*) near (blind* or mask*)
29 TG=animal
30 TG=human
31 (TG=animal) not (TG=human)
32 (#1 or #9 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #28) not #31
33 pulmonary
34 arter*
35 flotation
36 catheter*
37 (pulmonary arter*) near (flotation or catheter*)
38 right?heart
39 right
40 heart
41 swan?ganz
42 swan
43 ganz
44 ((right?heart) or (right heart) or (swan?ganz) or (swan ganz)) near catheter*
45 "Catheterization-Swan-Ganz"/all subheadings
46 (#37 or #44 or #45) and #32
47 #46
48 (COMMENT or EDITORIAL) in PT
49 #47 not ((COMMENT or EDITORIAL) in PT)

Appendix 3

Data collection form for systematic review

Data Collection Form

(Final version 19 Oct 2001)

PAC-Man in adult intensive care (clinical and cost effectiveness)

Study identifier _____ **Author** _____

Year of publication _____ **Journal** _____

Country (where study performed) _____

Reviewer _____

Funding source: government pharmaceutical private
unfunded unclear

Verification/selection of study eligibility (circle one)

Was randomised	yes	no	unclear
Used usual care control groups	yes	no	unclear
Involved adults (16 years of age or above)	yes	no	unclear
Included patients admitted electively for pre-operative optimisation	yes	no	unclear
Included patients with a PAC already in situ from elsewhere	yes	no	unclear
Included brain dead patients with a catheter placed for organ support prior to donation	yes	no	unclear
Gives data on mortality	yes	no	unclear
Gives data on morbidity	yes	no	unclear
Gives data on complications with PAC	yes	no	unclear
Gives data on cost of PAC Management	yes	no	unclear

Inclusion criteria

Exclusion criteria

Methods

Randomisation and allocation concealment method

A = Clearly adequate: Centralised randomisation by telephone; randomisation scheme controlled by pharmacy; numbered or coded identical containers administered sequentially; on site computer system which can only be accessed after entering the characteristics of an enrolled participant; sequentially numbered, sealed, opaque envelopes.

B = Possibly adequate: Sealed envelopes but not sequentially numbered or opaque; list of random numbers read by someone entering patient into trial (open list); a trial in which the description suggests adequate concealment, but other features are suspicious (for example: markedly unequal controls and trial groups; stated random, but unable to obtain further details).

C = Clearly inadequate: Any allocation procedure transparent before assignment (for example: an open list of random numbers, alteration, date of birth, day of week, case record number).

D = Not described

Average duration of follow-up: _____

Participants

Number of subjects screened _____

Total number of eligible subjects _____ Number of subjects enrolled _____

Number of subjects completed trial _____

	All	Group 1	Group 2	Group 3
Mean age				
Age range or variability				

Setting: (circle all that apply)
medical surgical cardiac

Intervention (state type of flow measurement if used)

Group 1

Group 2

Group 3

Drop-outs

Intervention Group	Total no. randomised	Total on assigned treatment	Reasons

Outcomes and results

	No. Group 1 (*n* =)	**No. Group 2 (*n* =)**	**No. Group 3 (*n* =)**
Death			
Morbidities (total no.)			
Morbidities (no. of patients)			
Complications (total no.)			
Complications (no. of patients)			
Cost (+ variability)			
Hosp. LOS (+ variability)			
ICU LOS (+ variability)			

How was variability reported?
a. Standard deviation
b. Standard error mean
c. range
d. other
e. not given

How was statistical significance reported?
a. confidence interval
b. *p* value
c. other
d. not given

Is interim outcome data available (i.e. data reported after start and before end of study) and if so, which outcome?

_____

Changes in protocol during study: _____

_____

Comments:

_____

_____

_____

_____

_____

_____

_____

_____

Anything useful in reference list **yes** **no**
(if yes *)

Appendix 4

Patient information sheet

PATIENT INFORMATION SHEET

A Study to investigate whether the use of the Pulmonary Artery Catheter is of Benefit to Patients in Intensive Care.

Principal Local Investigator _____

You are being invited to take part in a research study while you are here as a patient in the intensive care unit. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please read the following information carefully and, if you wish, to discuss it with your relatives or friends. Ask us if there is anything that is unclear or if you would like more information. Thank you for reading this.

What is the purpose of the study?
The pulmonary artery catheter is a measuring instrument which has been used in intensive care patients for thirty years to assess the heart's performance. This catheter is fed into one of the big blood vessels within the chest where it can remain for up to several days. The measurements the catheter provides can help the doctors and nurses to keep track of the patient's condition.

At present, we do not know whether or not the use of the pulmonary artery catheter provides long-term benefit. This level of uncertainty is so high that the Department of Health have agreed to fund a national study involving more than 5000 Intensive Care patients in many centres around the UK. This will compare the progress of patients who either receive or do not receive the pulmonary artery catheter. The London MultiCentre Research Ethics Committee as well as your local Hospital Ethics Committee have reviewed and approved the study.

Why have I been chosen?
At this point in time, your doctors would normally consider placing a pulmonary artery catheter into you to obtain the additional information felt necessary to guide your care.

Do I have to take part?
It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you 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.

What will happen to me if I take part?
As we do not know which way of treating patients is best, we need to make comparisons. People are put into groups and then compared. The groups are selected by a computer that will decide on a chance basis (as if it were tossing a coin) whether you will receive the catheter or not. For those not chosen to receive the catheter, other techniques may be used instead. Your progress will be closely followed to see whether or not use of the catheter turns out to be beneficial.

What do I have to do?
All other care will continue in the usual manner. If you are in the group that does not receive the catheter, and the doctor in charge of your care considers that there is an overwhelming need at any subsequent point of time to insert this device, then you will receive the catheter.

What are the possible risks and benefits of taking part?
There are risks associated with the placing and the use of this catheter that may be more important than the information it supplies. These risks include bleeding from the blood vessels or damage to the heart valves through which it passes, infection and abnormal heart rhythms.

On the other hand, if the catheter is not used, there may be risks resulting from the doctors not having the information it would have supplied. Some of this information cannot be obtained in any other way, even with alternative devices.

What if something goes wrong?
This study is investigating an established procedure rather than a new technique. Indeed, half the patients participating in this study will not receive the pulmonary artery catheter which, in normal circumstances, would have occurred. If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms will be available to you.

Will my taking part in this study be kept confidential?
All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it.

What will happen to the results of the research study?
The study is estimated to take one year, commencing in Spring 2001. It is hoped to publish the results by winter 2002. If you would like a copy of the published results, please contact the Principal Local Investigator (name given above)

Contact for further information
If you would like further information, please feel free to contact

Dr _____, the consultant leading the study on this unit.

Appendix 5

Patient consent form

Centre Number:

Study Number:

Patient Identification Number for this trial:

PATIENT CONSENT FORM

Title of Project: A Study to investigate whether the use of the Pulmonary Artery Catheter is of Benefit to Patients in Intensive Care

Name of Researcher: _____

Please initial box

1. I confirm that I have read and understand the information sheet dated _____ (version .....) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that sections of any of my medical notes may be looked at by responsible individuals from the intensive care unit where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
4. I agree to take part in the above study. ☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Person taking consent (if different from researcher)	Date	Signature
_____	_____	_____
Researcher	Date	Signature

1 copy for patient; 1 for researcher; 1 to be kept with hospital notes

Appendix 6

Relative's information sheet

RELATIVE'S INFORMATION SHEET

A Study to investigate whether the use of the Pulmonary Artery Catheter is of Benefit to Patients in Intensive Care.

Principal Local Investigator _____

We would like your relative to take part in a research study while he/she is a patient in this intensive care unit. Unfortunately, your relative is not well enough to be able to decide for him/herself whether or not to participate. Legally, you cannot provide consent on his/her behalf. However, we ask you to read the patient's information sheet carefully and give your opinion as to whether or not you think your relative would have objected to taking part in this medical research.

When your relative has regained consciousness and has the ability to understand the purpose of this study, we will seek his/her permission retrospectively.

If you have further questions either now or at any time subsequently, please feel

free to contact Dr _____, the consultant leading the study on this unit.

Thank you for your time in considering this request.

Appendix 7

Relative's form

Centre Number:

Study Number:

Patient Identification Number for this trial:

RELATIVE'S FORM

Title of Project: A Study to investigate whether the use of the Pulmonary Artery Catheter is of Benefit to Patients in Intensive Care

Name of Researcher: _____

Please initial box

1. I confirm that I have read and understand the information sheet dated _____ (version .....) for the above study and have had the opportunity to ask questions. ☐
2. I understand that I cannot legally give consent for my relative to participate in the study. However, in my opinion, he/she would not have objected to taking part. ☐
3. I understand that relevant sections of any of my relative's medical notes may be looked at by responsible individuals involved with the study. In my opinion, he/she would not have objected to these individuals having access to his/her records. ☐

_____	_____	_____
Name of Relative	Date	Signature

Relationship to patient _____

_____	_____	_____
Name of Person informing relative (if different from researcher)	Date	Signature

_____	_____	_____
Researcher	Date	Signature

1 copy for patient; 1 for researcher; 1 to be kept with hospital notes

Appendix 8

Patient information sheet for retrospective consent

RETROSPECTIVE CONSENT
PATIENT INFORMATION SHEET

A study to investigate whether the use of the Pulmonary Artery Catheter is of Benefit to Patients in Intensive Care

Principal Local Investigator _____

During your stay in the intensive care unit you took part in a research study that is currently taking place in more than 70 intensive care units throughout the UK. It is important for you to understand why the research is being done and what it involves. Please read the following information carefully and, if you wish, discuss it with your relatives or friends. Ask if there is anything that is unclear or if you would like any more information. Thank you for reading this.

What is the purpose of the study?
The pulmonary artery catheter is a measuring instrument, which has been used in intensive care patients for thirty years to assess the heart's performance. This catheter is fed into one of the big blood vessels within the chest where it can remain for up to several days. The measurements the catheter provides may help doctors and nurses to keep track of the patient's condition.

At present, we do not know whether or not the use of the pulmonary artery catheter provides long-term benefit. The potential risks of insertion of the catheter, for example bleeding, may or may not be outweighed by the information that it provides. This level of uncertainty is so high that the Department of Health have given funding for this national study involving more than 5000 Intensive Care patients in many centres around the UK. The study will compare the progress of patients who either receive or do not receive the pulmonary artery catheter. The London Multicentre Research Ethics Committee, as well as your Local Hospital Ethics Committee, have reviewed and approved the study.

Why was I chosen and what happened to me?
During your stay in the intensive care unit doctors considered placing a pulmonary artery catheter. As we do not know which way of treating patients is best you were entered into the study and allocated to one of two groups. The groups were allocated on a chance basis by a computer (as if tossing a coin) so that you had a 50% chance of receiving a catheter or not. For those in the group not receiving a catheter other monitoring techniques may have been used instead. All patients, whether they had a pulmonary artery catheter placed or not, received all other care in the usual manner and both groups received careful monitoring. If you did not receive a catheter, the doctors who cared for you during your stay could have inserted the device at any point if they had felt that there was an overwhelming need.

What if something had gone wrong?
The study is investigating an established procedure rather than a new technique. Indeed, half the patients who participate in the study will not receive a pulmonary artery catheter, which, in normal circumstances, would have occurred. If you were to have been harmed by taking part in this research project, there are no special compensation arrangements. If you had been harmed due to someone's negligence, then you may have grounds for legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of the study, the normal National Health Service complaints mechanisms is available to you.

What happens now?
Your remaining stay in hospital will continue as normal. There is no need for you to undergo any special tests or investigations or for you to be inconvenienced in any way.

Why are you explaining this to me?
As part of the study routine medical information was collected. If you give your permission, the collected information can be used and you will be asked to sign a consent form. If you do not wish the information to be used then you do not have to give your consent and the data collected for the study will be destroyed. If you decide not to give permission you do not have to give a reason and the standard of care you receive will not be affected. Information in your hospital record remains unaffected.

Will my taking part be kept confidential?
All the information that has been collected about you during the course of the research study will be kept strictly confidential. Any information about you that leaves the hospital will have your name and address removed so that you cannot be recognised from it.

What will happen to the results of the research study?
The study is estimated to take one year and it is hoped that the results will be published by winter 2002. If you would like a copy of the published results, please contact the Principal

Local Investigator _____ who is the consultant leading the study at the intensive care unit.

Appendix 9

Patient incapacity to provide consent form

PATIENT INCAPACITY TO PROVIDE RETROSPECTIVE INFORMED CONSENT

(FOR THE USE OF THEIR DATA)

Project title: A Study to investigate whether the use of the Pulmonary Artery Catheter is of Benefit to Patients in Intensive Care

Patient details

Initials: _____

Date of birth: _____

Date of randomisation to PAC-Man Study: _____

Patient Study Number: _____

Please state clearly the reasons why the patient is unable to provide retrospective informed consent:

_____

_____

_____

_____

_____

_____

_____	_____	_____
Name of clinician	Signature	Date
_____	_____	_____
Name of Researcher (if different)	Signature	Date

1 copy placed in the hospital notes, 1 copy for researcher, 1 copy for the Local Research Ethics Committee

Appendix 10

Data collection forms for the RCT

Centre Number: ☐☐☐☐

STUDY ENTRY

PACMan

Please complete before you telephone the Randomisation Service

1. Consent obtained from patient? **Yes** ☐1 **No** ☐2
If **NO,** signed assent should be obtained, as soon as possible from a relative

Inclusion Criteria

2. Is the patient deemed by the clinician to require management with a pulmonary artery catheter? **Yes** ☐1 **No** ☐2 → Exclude

Exclusion Criteria

3. Is the patient less than 16 years of age? **Yes** ☐1 → Exclude **No** ☐2

4. Has the patient been admitted electively prior to surgery for pre-operative optimisation? **Yes** ☐1 → Exclude **No** ☐2

5. Does the patient have a pulmonary artery catheter already in situ? **Yes** ☐1 → Exclude **No** ☐2

6. Has the patient been entered into the PAC-Man Study previously during this hospital admission? **Yes** ☐1 → Exclude **No** ☐2

7. Is the patient brain stem dead or currently being considered for brain stem death testing? **Yes** ☐1 → Exclude **No** ☐2

8. Date of birth ☐☐/☐☐/☐☐☐☐ *(dd/mm/yyyy)* **9.** Sex: Male ☐1 Female ☐2

10. Patient's initials ☐☐☐

Pre-Randomisation Data Collection

11. Which option below **best** describes the patient's major, presumptive, clinical syndrome? *(tick (✓) **one** box only)*

a. Acute respiratory failure ☐1
b. Multi-organ dysfunction ☐2
c. Decompensated (congestive) heart failure ☐3
d. Other *(please specify)* ☐4
☐4

12. Was the patient admitted to your ICU directly from theatre/recovery in your hospital? **Yes** ☐1 **No** ☐2
If **YES,** was the surgery? *(tick (✓) **one** box only)*

a. Emergency *(immediate surgery, where resuscitation is simultaneous with surgical treatment)* ☐1
b. Urgent *(surgery as soon as possible after resuscitation)* ☐1
c. Scheduled *(early surgery but not immediately life saving)* ☐2
d. Elective *(surgery at a time to suit both patient and surgeon)* ☐2

If the patient is not excluded, please telephone the Randomisation Service
Telephone: 0800 387 444

Patient Study Number: ☐☐☐☐☐

13. Please indicate to which group the patient has been allocated by the Randomisation Service *(tick (✓) **one** box only)*

To be managed with a pulmonary artery catheter ☐1
Not to be managed with a pulmonary artery catheter ☐2

Person completing form:

Name (PRINT): _____ Signature: _____

Date: ☐☐/☐☐/☐☐☐☐ *(dd/mm/yyyy)* Time of randomisation: ☐☐:☐☐ *(24 hour clock)*

PACMAN/SE/1/901

At Time of Randomisation

Q14 Organs being monitored/supported at time of randomisation

Advanced respiratory system monitoring/support is indicated by **one or more** of the following:
- Mechanical ventilatory support (excluding mask CPAP or non-invasive methods eg. mask ventilation)
- Extracorporeal respiratory support

Basic respiratory system monitoring/support is indicated by **one or more** of the following:
- More than 50% oxygen by fixed performance mask
- The potential for deterioration to the point of needing advanced respiratory support
- Physiotherapy to clear secretions at least two hourly, whether via a tracheostomy, minitracheostomy or in absence of an artificial airway
- Patients recently extubated after a prolonged period of intubation and mechanical ventilation
- Mask CPAP or non-invasive ventilation
- Patients who are intubated to protect the airway but needing no ventilatory support and who are otherwise stable

Circulatory system monitoring/support is indicated by **one or more** of the following:
- Vasoactive drugs used to support arterial pressure or cardiac output
- Circulatory instability due to hypovolaemia from any cause
- Patients resuscitated following cardiac arrest where intensive care is considered clinically appropriate
- Intra-aortic balloon pumping

Neurological system monitoring/support is indicated by **one or more** of the following:
- Central nervous system depression, from whatever cause, sufficient to prejudice the airway and protective reflexes
- Invasive neurological monitoring eg. ICP, jugular bulb sampling

Renal system monitoring/support is indicated by:
- Acute renal replacement therapy (haemodialysis, haemofiltration etc)

Q15

f. Severe chronic lung disease defined by **one or more** of the following:
- FEV_1 less than 35% predicted, or;
- FEV_1/VC less than 50% predicted, or;
- Chronic hypercapnia ($PaCO_2$ greater than 6.6 kPa/45 mmHg) and/or chronic hypoxaemia (PaO_2 less than 7.3 kPa/55 mmHg) on FIO_2 of 0.21, or;
- Radiographic evidence of over-inflation or chronic interstitial infiltration, or;
- Hospitalisation within the past six months for respiratory failure ($PaCO_2$ greater than 6.6 kPa/50 mmHg or PaO_2 less than 7.3 kPa/55 mmHg or SaO_2 less than 88% on FIO_2 of 0.21), or;
- Chronic restrictive, obstructive, neuromuscular, chest wall or pulmonary vascular disease resulting in severe exercise restriction eg. unable to climb stairs or perform household duties, secondary polycythaemia, severe pulmonary hypertension (mean pulmonary artery pressure greater than 40 mmHg) or ventilator dependency.

i. Body Mass Index = Weight in Kg/(Height in m)^2

Q22 Assessment of Glasgow Coma Score

- If sedated/paralysed for the whole time period in your ICU prior to randomisation, tick box
- Only Glasgow Coma Scores assessed when the admission is free from the effects of sedative and/or paralysing or neuromuscular blocking agents are valid
- Assessment of the Glasgow Coma Score:

The best eye opening response	
Spontaneous	4
To verbal command	3
To pain	2
No response	1

The best motor response	
Obeys verbal command	6
Localises pain	5
Flexion withdrawal	4
Flexion-abnormal/decorticate rigidity	3
Extension/decerebrate rigidity	2
No response	1

The best verbal response	
Orientated and converses	5
Disorientated and converses	4
Inappropriate words	3
Incomprehensible sounds	2
No response	1

If an admission is **intubated**, use clinical judgement to score verbal response as follows:

Appears orientated	5
Responsive but ability to converse questionable	3
Generally unresponsive	1

Centre Number: ☐☐☐☐
Patient Initials: ☐☐☐
Patient Study Number: ☐☐☐☐☐

AT TIME OF RANDOMISATION

PACMan

14. Please indicate the organs being monitored/supported at the time of randomisation

a. Advanced respiratory monitoring/support	**Yes** ☐	**No** ☐
b. Basic respiratory monitoring/support	**Yes** ☐	**No** ☐
c. Circulatory monitoring/support	**Yes** ☐	**No** ☐
d. Neurological monitoring/support	**Yes** ☐	**No** ☐
e. Renal monitoring/support	**Yes** ☐	**No**

15. Please indicate the presence, or not, of any of the following conditions at the time of randomisation

a. Clinical evidence of left sided heart failure (elevated left atrial pressure)	**Yes** ☐	**No** ☐
b. Chest x-rays showing new bilateral infiltrates consistent with pulmonary oedema during the 48 hours prior to randomisation	**Yes** ☐	**No** ☐
c. Burns on greater than 40% of body surface area	**Yes** ☐	**No** ☐
d. Bone marrow transplantation including autologous transplantation	**Yes** ☐	**No** ☐
e. Acute myocardial infarction in the last 30 days	**Yes** ☐	**No** ☐
f. Severe chronic lung disease	**Yes** ☐	**No** ☐
g. Neuromuscular disease that precludes spontaneous ventilation	**Yes** ☐	**No** ☐
h. Vasculitis with diffuse alveolar haemorrhage (Wegener's or similar)	**Yes** ☐	**No** ☐
i. Morbid obesity (Body Mass Index greater than 40kg m^{-2})	**Yes** ☐	**No** ☐
j. Pregnancy	**Yes** ☐	**No** ☐

16. Which option below best describes the primary reason for inserting a pulmonary artery catheter? *(tick (✓) one box only)*

a. To guide inotropic/vasoactive drug treatment in a patient not yet receiving these drugs	☐
b. To guide inotropic/vasoactive drug treatment in a patient already receiving these drugs	☐
c. To guide fluid/diuretic/haemofiltration treatment	☐
d. To guide treatment of oliguria	☐
e. To guide treatment of a metabolic acidosis	☐
f. To diagnose and/or guide treatment of the cause for failure to wean from mechanical ventilation	☐
g. Other diagnostic reasons (intra-cardiac shunt, pulmonary hypertension etc)	☐

Please give the most recent ie. last recorded values prior to randomisation

17. Arterial blood gas value (from the **same** sample)

FIO_2	☐.☐☐	
PaO_2	☐☐.☐ kPa **or**	☐☐☐ mmHg
$PaCO_2$	☐☐.☐ kPa **or**	☐☐☐ mmHg
pH/H^+	☐.☐☐ pH **or**	☐☐☐ nmol l^{-1}

Please give the most recent ie. last recorded values prior to randomisation

18. Haemoglobin (g dl^{-1})	☐☐.☐	
19. Platelet count ($\times 10^3 mm^{-3}$)	☐☐☐	
20. Total serum bilirubin (μmol l^{-1})	☐☐☐	
21. Serum creatinine (μmol l^{-1})	☐☐☐☐	
22. Total Glasgow Coma Score	☐☐ **or** tick if sedated/paralysed	☐
23. Mean arterial blood pressure (mmHg)	☐☐☐	
24. Vasopressors administered for at least one hour?	**Yes** ☐	**No** ☐

If **YES**, please record the maximum dose in the **last hour**

Name of drug: Maximum dose		($\mu g\ kg^{-1}\ min^{-1}$):
Name of drug: Maximum dose		($\mu g\ kg^{-1}\ min^{-1}$):
Name of drug: Maximum dose		($\mu g\ kg^{-1}\ min^{-1}$):

Please continue on second sheet ➔

Centre Number: ☐☐☐☐
Patient Initials: ☐☐☐
Patient Study Number: ☐☐☐☐☐

AT TIME OF RANDOMISATION
(continuation sheet)

PACMan

FOR PATIENTS RANDOMISED NOT TO BE MANAGED WITH A PULMONARY ARTERY CATHETER → go to Q32 on page 7

FOR PATIENTS RANDOMISED TO BE MANAGED WITH A PULMONARY ARTERY CATHETER

25. Pulmonary artery catheter inserted? **Yes** ☐ → go to Q26
If NO, *(tick (✓) **one** box only)* **No** ☐
Patient died ☐ → go to Q32
Consent/Assent withdrawn ☐ → complete **Withdrawal From Study** form (page 15)
Other ☐ → complete **Protocol Violation** form (page 15) and then go to Q32

26. Date pulmonary artery catheter insertion completed ☐☐/☐☐/☐☐☐☐ *(dd/mm/yyyy)*
27. Time pulmonary artery catheter insertion completed ☐☐:☐☐ *(24 hour clock)*

28. Date of post-insertion chest x-ray ☐☐/☐☐/☐☐☐☐ *(dd/mm/yyyy)*
29. Time of post-insertion chest x-ray ☐☐:☐☐ *(24 hour clock)*

30. Did any of the following complications occur as a direct result of the pulmonary artery catheter being inserted?

a. Local bleeding from insertion site for more than one hour	**Yes** ☐	**No** ☐
b. Haematoma at insertion site	**Yes** ☐	**No** ☐
c. Arterial puncture	**Yes** ☐	**No** ☐
d. Arrhythmias requiring treatment within one hour of insertion	**Yes** ☐	**No** ☐
e. Pneumothorax	**Yes** ☐	**No** ☐
f. Haemothorax	**Yes** ☐	**No** ☐
g. Pericardial tamponade	**Yes** ☐	**No** ☐
h. Other *(please specify)*	**Yes** ☐	**No** ☐

31. Did any of the following changes in the management of the patient occur within two hours as a direct result of the pulmonary artery catheter being inserted?

a. Infusion of 200ml or more of fluid above maintenance in one hour	**Yes** ☐	**No** ☐
b. Introduction of a vasoactive or inotropic drug, including inhaled vasodilators (eg. NO)	**Yes** ☐	**No** ☐
c. Change in the dose of vasoactive or inotropic drug of greater than 25%	**Yes** ☐	**No** ☐
d. Previously unscheduled haemofiltration or dialysis session	**Yes** ☐	**No** ☐
e. Additional diuretic therapy	**Yes** ☐	**No** ☐
f. Previously unscheduled surgical or drainage procedure	**Yes** ☐	**No** ☐
g. Previously unscheduled imaging (other than a chest x-ray)	**Yes** ☐	**No** ☐
h. Other *(please specify)*	**Yes** ☐	**No** ☐

Person completing form:
Name (PRINT): _____ Signature: _____
Date: ☐☐/☐☐/☐☐☐☐ *(dd/mm/yyyy)*

Admission to ICU

The Admission to ICU form should be completed **for the first 24 hours in your ICU**, regardless of the day of randomisation
If the patient stays less than 24 hours, please complete for the period in your ICU

Q35 Past Medical History

Portal hypertension
- evidence of portal hypertension is the presence of oesophageal or gastric varices demonstrated by surgery, imaging or endoscopy or the demonstration of retrograde splenic venous flow by ultrasound
- do not include gastrointestinal bleeding without evidence of portal hypertension

Hepatic encephalopathy
- episodes of hepatic encephalopathy, Grade 1 or greater

Grade 0	No abnormality detected
Grade 1	Slowness in cerebration, intermittent mild confusion and euphoria
Grade 2	Confused most of the time, increasing drowsiness
Grade 3	Severe confusion, rousable, responds to simple commands
Grade 4	Unconscious, responds to painful stimuli

Very severe cardiovascular disease
- fatigue, claudication, dyspnoea or angina **at rest**, where any activity increases symptoms, symptoms must be due to myocardial or peripheral vascular disease, functionally, this patient cannot stand alone, walk slowly or dress without symptoms

Severe respiratory disease
- has permanent shortness of breath **with light activity** due to pulmonary disease, functionally, this patient is unable to work and has shortness of breath performing most normal activities of daily living eg. walking 20 metres on level ground, walking slowly in the house, climbing one flight of stairs, dressing or standing

Home ventilation
- has used or uses home ventilation
- ventilation is defined as where all or some of the breaths or a portion of the breaths (pressure support) are delivered by a mechanical device, ventilation can be simply defined as a treatment where some or all of the energy required to increase lung volume during inspiration is supplied by a mechanical device
- CPAP is excluded

Chronic renal replacement
- currently requires chronic renal replacement therapy (either chronic haemodialysis, chronic haemofiltration or chronic peritoneal dialysis) for irreversible renal disease

AIDS
- HIV positive **with** clinical complications
- clinical complications include pneumocystis carinii pneumonia, Karposi's sarcoma, lymphoma, tuberculosis and toxoplasma infection
- do not include AIDS-related complex or HIV positivity alone

Steroid treatment
- has received ≥0.3 mg kg^{-1} prednisolone or an equivalent dosage of another corticosteroid, **daily** for the six months prior to admission to your unit

Radiotherapy
- has received externally administered radiotherapy, **excluding** all of the following: radiotherapy for non-invasive skin tumours; enteral or parenteral radioisotope therapy; radioactive implants; radiotherapy for prevention of heterotopic bone formation

Chemotherapy
- has received drug treatment resulting in a lower resistance to infection
- examples include drug treatment for malignancy, vasculitides, rheumatoid arthritis, inflammatory bowel disease etc.

Metastatic disease
- has distant (not regional lymph node) metastases, documented by surgery, imaging or biopsy

Lymphoma
- has active lymphoma, documented by surgery, imaging or biopsy

Congenital immunohumoral or cellular immune deficiency
- has a documented congenital immunohumoral or congenital cellular immune deficiency state
- examples include Common Variable Immunodeficiency (CVID), agammaglobulinaemia including X linked (XLA), severe combined immuno deficiency (SCID), Chronic Granulomatous Disease, IgA deficiency, IgG deficiency, functional antibody deficiency, hyper IgE syndrome, Wiskott Aldrich syndrome, Chronic Mucocutaneous Candidiasis (CMCC), Di George syndrome, Ataxia Telangiectasia, Leucocyte Adhesion Defect, Complement deficiencies, C1 Esterase inhibitor deficiency, Kostmann's syndrome

Q36 Primary reason for admission to your unit

- **Body system:** eg. respiratory, cardiovascular, poisoning, traumatic.
- **Anatomical site:** eg. lungs, upper airway and trachea, coronary arteries, heart valves, thoracic aorta, stomach, oesophagus, endocrine pancreas etc.
- **Physiological/Pathological process:** eg. haemorrhage, infection, trauma, accidental intoxication or poisoning, self-intoxication or poisoning, inflammation, obstruction etc.
- **Condition:** eg. lung collapse or atelectasis, haemorrhage, infection, bacterial pneumonia, cervical cord injury, myxoma, trauma to aortic valve etc.
- **ICNARC Coding Method:** if you are using the ICNARC Coding Method, please enter the diagnostic code

Centre Number: ☐☐☐☐
Patient Initials: ☐☐☐
Patient Study Number: ☐☐☐☐☐

ADMISSION TO ICU

PACMan

32. Is your ICU part of ICNARC (ie. participating in the Case Mix Programme)? **Yes** ☐ **No** ☐ → go to Q33 **Don't know** ☐ → go to Q33

If **YES**, Case Mix Programme Admission Number ☐☐☐☐☐☐☐☐

Postcode: ☐☐☐☐☐☐☐☐ → go to Q55

33. Date of admission to your ICU ☐☐/☐☐/☐☐☐☐ *(dd/mm/yyyy)*

34. Time of admission to your ICU ☐☐:☐☐ *(24 hour clock)*

35. Past medical history of one or more of the conditions listed below *(✓ tick **one** box on **each** line)*

Evidence that condition existed or therapy received in six months prior to admission to your ICU and documented, either prior to admission or at admission to your ICU

Biopsy proven cirrhosis	**Yes** ☐	**No** ☐
Portal hypertension	**Yes** ☐	**No** ☐
Hepatic encephalopathy	**Yes** ☐	**No** ☐
Very severe cardiovascular disease	**Yes** ☐	**No** ☐
Severe respiratory disease	**Yes** ☐	**No** ☐
Home ventilation	**Yes** ☐	**No** ☐
Chronic renal replacement	**Yes** ☐	**No** ☐
AIDS	**Yes** ☐	**No** ☐
Steroid treatment (**daily** for six months)	**Yes** ☐	**No** ☐
Radiotherapy	**Yes** ☐	**No** ☐
Chemotherapy	**Yes** ☐	**No** ☐
Metastatic disease	**Yes** ☐	**No** ☐
Acute myelogenous/lymphocytic leukaemia or multiple myeloma	**Yes** ☐	**No** ☐
Chronic myelogenous/lymphocytic leukaemia	**Yes** ☐	**No** ☐
Lymphoma	**Yes** ☐	**No** ☐
Congenital immunohumoral or cellular immune deficiency state	**Yes** ☐	**No** ☐

36. Primary reason for admission to your unit *(please describe)*

Body system: _____

_____

Anatomical site: _____

_____

Physiological/Pathological process: _____

_____

Condition: _____

_____

OR Code with ICNARC Coding Method: ☐☐.☐☐.☐☐.☐☐.☐☐.☐☐

Please continue on second sheet →

Admission to ICU

The Admission to ICU form should be completed **for the first 24 hours in your ICU** regardless of the day of randomisation
If the patient stays less than 24 hours, please complete for the period in your ICU

Q37 & 38 Central/Non-central Temperature

- Tympanic membrane, nasopharyngeal, oesophageal, rectal, pulmonary artery, bladder are considered as **central** temperature measurement sites

Q41 Heart Rate

- For admissions who are paced, record the actual measured ventricular rate
- Ventricular rates should not be recorded for any admissions during periods of iatrogenic disturbance eg. physiotherapy, turning, periods of crying etc

Q42 & 43 Non-ventilated/Ventilated Respiratory Rate

- A respiratory rate is defined as ventilated where all or some of the breaths or a portion of the breaths (pressure support) are delivered by a mechanical device, ventilation can be simply defined as a treatment where some or all of the energy required to increase lung volume during inspiration is supplied by a mechanical device
- High frequency and jet ventilators, negative pressure ventilators and BIPAP are considered as ventilated
- Hand ventilation by a member of your team is considered as ventilated
- CPAP and ECMO are considered as **not** ventilated
- For admissions who are ventilated, the respiratory rate should account for both ventilated and spontaneous breaths in a minute

Q45 Intubated arterial blood gas with highest FIO2

- Intubated is defined as either a laryngeal mask or an endotracheal, endobronchial or tracheostomy tube in place

Q46-51 Serum sodium/potassium/creatinine/haematocrit/haemoglobin/white blood cell count

- Laboratory results only, performed either in the departments of Clinical Chemistry or Haematology or in near patient testing laboratories with formal quality control programmes in operation. For white blood cell count, the effects if steroids, inotropes and splenectomy are ignored

Q52 Urine output

- No account is taken of the effect of diuretics

Q53 Assessment of Glasgow Coma Score

- Only Glasgow Coma Scores assessed when the admission is free from the effects of sedative and/or paralysing or neuromuscular blocking agents are valid
- Assessment of the Glasgow Coma Score:

The best eye opening response	
Spontaneous	4
To verbal command	3
To pain	2
No response	1

The best motor response	
Obeys verbal command	6
Localises pain	5
Flexion withdrawal	4
Flexion-abnormal/decorticate rigidity	3
Extension/decerebrate rigidity	2
No response	1

The best verbal response	
Orientated and converses	5
Disorientated and converses	4
Inappropriate words	3
Incomprehensible sounds	2
No response	1

If an admission is **intubated**, use clinical judgement to score verbal response as follows:

Appears orientated	5
Responsive but ability to converse questionable	3
Generally unresponsive	1

Centre Number: ☐☐☐☐
Patient Initials: ☐☐☐
Patient Study Number: ☐☐☐☐☐

ADMISSION TO ICU

(continuation sheet)

PACMan

Please complete for first 24 hours in your ICU (regardless of day of randomisation)

(If only one value available, record in lowest box)	Lowest	Highest
37. Central temperature (°C)	☐☐.☐	☐☐.☐
38. Non-central temperature (°C)	☐☐.☐	☐☐.☐
39. Systolic BP/paired diastolic BP (mmHg)	☐☐☐/☐☐☐	☐☐☐/☐☐☐
40. Diastolic BP/paired systolic BP (mmHg)	☐☐☐/☐☐☐	☐☐☐/☐☐☐
41. Heart rate (beats min^{-1})	☐☐☐	☐☐☐
42. Non ventilated respiratory rate (breaths min^{-1})	☐☐	☐☐
43. Ventilated respiratory rate (breaths min^{-1})	☐☐	☐☐

44. Arterial blood gas with **lowest** PaO_2 (from the **same** sample)	**Lowest** PaO_2	☐☐.☐ kPa **or** ☐☐☐ mmHg
	FIO_2	☐.☐☐
	$PaCO_2$	☐☐.☐ kPa **or** ☐☐☐ mmHg
	pH/H^+	☐.☐☐ pH **or** ☐☐☐ nmol l^{-1}
	Intubated	**Yes** ☐ **No** ☐
45. Intubated arterial blood gas with **highest** FIO_2 (from the **same** sample)	**Highest** FIO_2	☐.☐☐
	PaO_2	☐☐.☐ kPa **or** ☐☐☐ mmHg
	$PaCO_2$	☐☐.☐ kPa **or** ☐☐☐ mmHg
	pH/H^+	☐.☐☐ pH **or** ☐☐☐ nmol l^{-1}

	Lowest	Highest
46. Serum sodium (mmol l^{-1})	☐☐☐	☐☐☐
47. Serum potassium (mmol l^{-1})	☐☐.☐	☐☐.☐
48. Serum creatinine (μmol l^{-1})	☐☐☐☐	☐☐☐☐
49. Haematocrit (%)	☐☐	☐☐
50. Haemoglobin (g dl^{-1})	☐☐.☐	☐☐.☐
51. White blood cell count ($\times 10^9$ l^{-1})	☐☐☐.☐	☐☐☐.☐

52. Urine output (ml)

Total for first 24 hours	☐☐☐☐☐ mls
Total whilst in your ICU if stay less than 24 hours	☐☐☐☐☐ mls

53. Total Glasgow Coma Score (GCS)

Sedated/paralysed for whole of first 24 hours in your ICU	**Yes** ☐	→ please give most recent pre-sedation total GCS	☐☐
(if less than 24 hours, for whole period in your ICU)	**No** ☐	→ please give lowest total GCS	☐☐

54. Infection confirmed in first 24 hours in your ICU? **Yes** ☐ **No** ☐

If **YES,** *(✓ tick **one** box only)*

- ☐ Laboratory confirmed in first 24 hours
- ☐ Strongly suggested by evidence in first 24 hours

Person completing form:

Name (PRINT): _____ Signature: _____

Date: ☐☐/☐☐/☐☐☐☐ *(dd/mm/yyyy)*

Follow-up

Day of randomisation – complete for time period from time of randomisation to 23:59
Post randomisation days – complete for time period from 00:00 to 23:59

Q55 Organs being monitored/supported

Advanced respiratory system monitoring/support is indicated by **one or more** of the following:
- Mechanical ventilatory support (excluding mask CPAP or non-invasive methods eg mask ventilation)
- Extracorporeal respiratory support

Basic respiratory system monitoring/support is indicated by **one or more** of the following:
- More than 50% oxygen by fixed performance mask
- The potential for deterioration to the point of needing advanced respiratory support
- Physiotherapy to clear secretions at least two hourly, whether via a tracheostomy, minitracheostomy or in absence of an artificial airway
- Patients recently extubated after a prolonged period of intubation and mechanical ventilation
- Mask CPAP or non-invasive ventilation
- Patients who are intubated to protect the airway but needing no ventilatory support and who are otherwise stable

Circulatory system monitoring/support is indicated by **one or more** of the following:
- Vasoactive drugs used to support arterial pressure or cardiac output
- Circulatory instability due to hypovolaemia from any cause
- Patients resuscitated following cardiac arrest where intensive care is considered clinically appropriate
- Intra-aortic balloon pumping

Neurological system monitoring/support is indicated by **one or more** of the following:
- Central nervous system depression, from whatever cause, sufficient to prejudice the airway and protective reflexes
- Invasive neurological monitoring eg. ICP, jugular bulb sampling

Renal system monitoring/support is indicated by:
- Acute renal replacement therapy (haemodialysis, haemofiltration etc)

Indicator Dilution
- Such as PiCCO, Lidco or similar

Centre Number: ☐☐☐☐
Patient Initials: ☐☐☐
Patient Study Number: ☐☐☐☐☐

FOLLOW-UP

PACMan

55. Organ monitoring/support *(✓ tick appropriate boxes)*

Date:	Day of randomisation		Day 1 post-randomisation		Day 2 post-randomisation		Day 3 post-randomisation		Day 4 post-randomisation	
	Present Yes	No	Present Yes	No	Present Yes	No	Present Yes	No	Present Yes	No
Advanced respiratory support										
Basic respiratory support										
Circulatory support										
Neurological support										
Renal support										
Pulmonary artery catheter										
Trans-oesophageal Doppler										
Trans-thoracic Doppler										
Trans-thoracic bioimpedance										
Indicator dilution										
Echo-cardiogram										
Other flow measurement device										

Date:	Day 5 post- randomisation		Day 6 post-randomisation		Day 7 post-randomisation		Day 8 post-randomisation		Day 9 post-randomisation	
	Present Yes	No	Present Yes	No	Present Yes	No	Present Yes	No	Present Yes	No
Advanced respiratory support										
Basic respiratory support										
Circulatory support										
Neurological support										
Renal support										
Pulmonary artery catheter										
Trans-oesophageal Doppler										
Trans-thoracic Doppler										
Trans-thoracic bioimpedance										
Indicator dilution										
Echo-cardiogram										
Other flow measurement device										

Date:	Day 10 post- randomisation		Day 11 post-randomisation		Day 12 post-randomisation		Day 13 post-randomisation		Day 14 post-randomisation	
	Present Yes	No	Present Yes	No	Present Yes	No	Present Yes	No	Present Yes	No
Advanced respiratory support										
Basic respiratory support										
Circulatory support										
Neurological support										
Renal support										
Pulmonary artery catheter										
Trans-oesophageal Doppler										
Trans-thoracic Doppler										
Trans-thoracic bioimpedance										
Indicator dilution										
Echo-cardiogram										
Other flow measurement device										

If still in your ICU after 14 days post-randomisation, please use separate continuation sheet

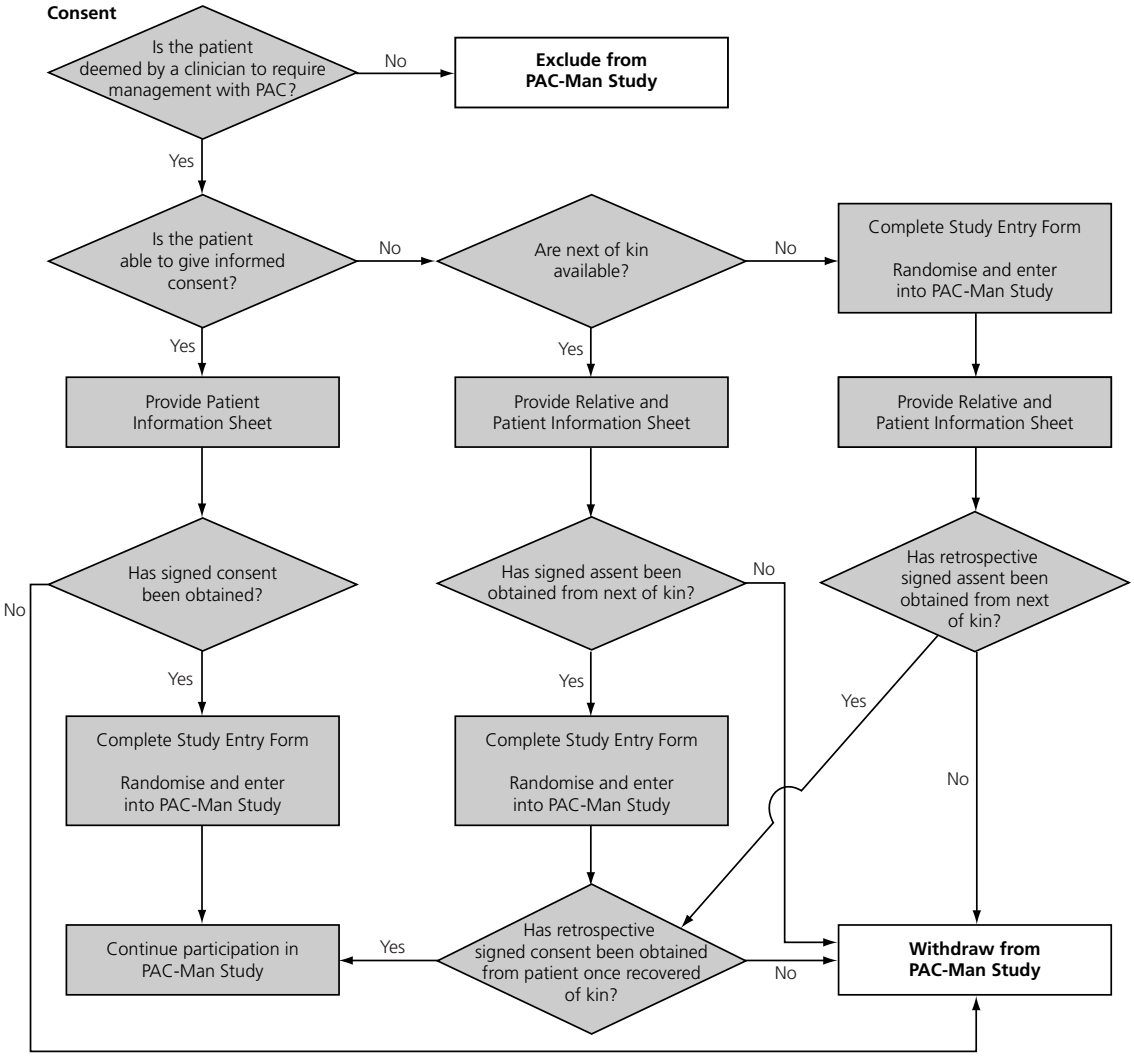
PACMAN/FU/1/901

Patient Data Booklet — *page 11*

Outcome

Q62 & 63 Removal of pulmonary artery catheter

- The date and time of removal of the pulmonary artery catheter should be for the **first** catheter that was inserted following randomisation even if it was subsequently replaced



Centre Number: ☐☐☐☐
Patient Initials: ☐☐☐
Patient Study Number: ☐☐☐☐☐

OUTCOME

PACMan

56. Status at discharge from your ICU

Alive ☐ → go to Q57
Dead ☐ → go to Q60

57. Date of discharge from your ICU ☐☐/☐☐/☐☐☐☐ *(dd/mm/yyyy)*
58. Time of discharge from your ICU ☐☐:☐☐ *(24 hour clock)*

59. Was the patient discharged directly to another hospital? **Yes** ☐ **No** ☐
If **YES,** please write the name of the hospital

60. Date of death ☐☐/☐☐/☐☐☐☐ *(dd/mm/yyyy)*
61. Time of death ☐☐:☐☐ *(24 hour clock)*

For patients randomised to be managed with a pulmonary artery catheter

62. Date **first** pulmonary artery catheter removed ☐☐/☐☐/☐☐☐☐ *(dd/mm/yyyy)*
63. Time **first** pulmonary artery catheter removed ☐☐:☐☐ *(24 hour clock)*

For patients randomised not to be managed with a pulmonary artery catheter

64. Was a pulmonary artery catheter inserted after randomisation? **Yes** ☐ → complete Protocol Violation form on page 15
No ☐

For ALL patients
Please note, **informed signed consent** must be obtained from **all** surviving patients. For most patients this will need to be done retrospectively, once the patient has regained consciousness.

65. Status at ultimate discharge from hospital

Alive ☐ → go to Q66
Dead ☐ → go to Q67

66. Date of discharge from hospital ☐☐/☐☐/☐☐☐☐ *(dd/mm/yyyy)* → go to Q69

67. Date of death in hospital ☐☐/☐☐/☐☐☐☐ *(dd/mm/yyyy)*
68. Time of death ☐☐:☐☐ *(24 hour clock)* → go to Q69

69. Has informed signed consent been obtained from the patient either before randomisation or retrospectively? **Yes** ☐ **No** ☐
If **NO**, specify reason:

Person completing form:
Name (PRINT): _____ Signature: _____
Date: ☐☐/☐☐/☐☐☐☐ *(dd/mm/yyyy)*

Once the booklet has been completed, the Top copy of pages 1–13 should be removed and returned to ICNARC in the self-addressed envelope supplied

Withdrawal From Study

The Withdrawal From Study form should be completed if the patient withdraws or is withdrawn from the study at any point during their hospital admission following randomisation

Protocol Violation

The Protocol Violation form should be completed for any patient who is not managed according to their allocated group, either intervention (to be managed with a pulmonary artery catheter) or control (not to be managed with a pulmonary artery catheter)

Centre Number: ☐☐☐☐
Patient Initials: ☐☐☐
Patient Study Number: ☐☐☐☐☐

WITHDRAWEL FROM STUDY/ PROTOCOL VIOLATION

PACMan

WITHDRAWAL FROM STUDY

Please complete if the patient was withdrawn from the PAC-Man Study after randomisation

Date of withdrawal from study ☐☐/☐☐/☐☐☐☐ *(dd/mm/yyyy)*
Time of withdrawal from study ☐☐:☐☐ *(24 hour clock)*

Reason for withdrawal from study *(tick ✓ appropriate boxes)*

Patient refused/withdrew Consent ☐
Relative refused/withdrew Assent ☐
Other reason *(please specify)* ☐

PROTOCOL VIOLATION

For patients randomised to be managed with a pulmonary artery catheter

Reason why the pulmonary artery catheter was **NOT** inserted?

For patients randomised NOT to be managed with a pulmonary artery catheter

Reason why the pulmonary artery catheter **WAS** inserted?

Person completing form:
Name (PRINT): _____ Signature: _____
Date: ☐☐/☐☐/☐☐☐☐ *(dd/mm/yyyy)*

Please return the **Top copy** of this form **as soon as possible** by fax or mail to:

PAC-Man Study
ICNARC
Tavistock House
Tavistock Square
London WC1H 9HR

Tel: 020 7388 2856
Fax: 020 7388 3759
email: icnarc@icnarc.org

Patient Data Booklet — *page 15*

Appendix 11

Augmented Care Period (ACP) data

Organ system monitoring/support was defined as follows according to the ACP criteria:

Advanced respiratory system monitoring/support is indicated by **one or more** of the following:

- mechanical ventilatory support (excluding mask continuous positive airway pressure (CPAP) or non-invasive methods, such as mask ventilation)
- extracorporeal respiratory support.

Basic respiratory system monitoring/support is indicated by **one or more** of the following:

- more than 50% oxygen by fixed performance mask
- the potential for deterioration to the point of needing advanced respiratory support
- physiotherapy to clear secretions at least 2-hourly, whether via a tracheostomy, minitracheostomy or in absence of an artificial airway
- patients recently extubated after a prolonged period of intubation and mechanical ventilation
- mask CPAP or non-invasive ventilation
- patients who are intubated to protect the airway but needing no ventilatory support and who are otherwise stable.

Circulatory system monitoring/support is indicated by **one or more** of the following:

- vasoactive drugs used to support arterial pressure or cardiac output
- circulatory instability due to hypovolaemia from any cause
- patients resuscitated following cardiac arrest where intensive care is considered clinically appropriate
- intra-aortic balloon pumping.

Neurological system monitoring/support is indicated by **one or more** of the following:

- central nervous system depression, from whatever cause, sufficient to prejudice the airway and protective reflexes
- invasive neurological monitoring, such as intra-cranial pressure monitoring, jugular bulb sampling.

Renal system monitoring/support is indicated by:

- acute renal replacement therapy (haemodialysis, haemofiltration, etc.).

Reference

NHS Executive. *Intensive and High Dependency Care Data Collection, (ACP data set).* London: Department of Health; 1997.

Appendix 12

Sepsis-related Organ Failure Assessment (SOFA)

The sepsis-related organ failure assessment (SOFA) score was created to describe quantitatively and objectively as possible the degree of organ dysfunction/failure over time in groups of patients or even in individual patients. There are two major applications of such a SOFA score:

- To improve understanding of the natural history of organ dysfunction/failure and the interrelation between the failure of the various organs.
- To assess the effects of new therapies on the course of organ dysfunction/failure. This could be used to characterise patients at entry (and even serve within the entry criteria) or to evaluate the effects of treatment.

The SOFA score is not designed to predict but to describe a sequence of complications in the critically ill. It assesses six organ systems (see below) and uses a score from 0 (normal) to 4 (most abnormal) for each organ. The worst values for each day are recorded.

Respiratory:	Oxygenation (PaO_2/FiO_2) with additional points for respiratory support
Coagulation:	Platelet count
Liver:	Serum bilirubin
Cardiovascular:	Mean arterial blood pressure with additional points for increasing doses of vasoactive drugs
Central nervous system:	Glasgow Coma Score
Renal:	Serum creatinine or urine output

Reference

Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, *et al.* The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996;**22**:707–10.

Appendix 13

Acute Physiology And Chronic Health Evaluation II (APACHE II)

APACHE II is a severity of disease classification system. It is a revised version of the prototype system, APACHE. The basis for APACHE's development was the hypothesis that the severity of acute disease (risk of death) can be measured by quantifying the degree of abnormality of multiple physiological variables at the commencement of treatment.

APACHE II uses a point score based upon initial values of 12 routine physiological measurements (see below), age and previous health status to provide a general measure of severity of disease. An increasing score (range 0–71) was closely correlated with the subsequent risk of hospital death for 5815 intensive care admissions from 13 hospitals in the original validation study.

When APACHE II scores are combined with an accurate description of disease, they can prognostically stratify acutely ill patients and assist investigators in comparing the success of new or differing forms of therapy.

The APACHE II severity of disease classification system has three components:

- Acute physiology score (APS)
  The APS is determined from the most deranged (worst) physiological value, such as the lowest blood pressure or the highest respiratory rate, during the initial 24 hours after admission to the ICU. The physiological variables are temperature, mean arterial blood pressure, heart rate, respiratory rate, oxygenation, arterial pH, serum sodium concentration, serum potassium concentration, serum creatinine concentration, haematocrit, white blood cell count and Glasgow Coma Score.
- Age
  Points are assigned for age.
- Chronic health
  Points are assigned if the patient has a history of severe organ system insufficiency or is immuno-compromised. More points are assigned for non-surgical or emergency surgical patients.

APACHE II score

The APACHE II score equals APS + age points + chronic health points.

APACHE II predicted risk of death

This combines the APACHE II score, surgical status and a weighting for diagnosis to produce a predicted mortality.

Reference

Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985;**13**:818–29.

Appendix 14

Data collection forms for the economic evaluation

PACMan

Pulmonary Artery Catheters
in Patient Management

CAPITAL EQUIPMENT QUESTIONNAIRE

This questionnaire asks about capital equipment in your unit for the financial year 2002/03 (1 April 2002 to 31 March 2003)

Centre Number:

Hospital Name:

Unit type:
(please tick (✓) appropriate)

☐ ICU ☐ ICU/HDU

☐ ICU/CCU ☐ ICU/HDU/CCU

☐ Other (describe)

If you have any queries, please contact:

Ms Katherine Stevens Tel: 0114 2220841 email: k.stevens@sheffield.ac.uk
or Mr Chris McCabe Tel: 0114 2220728 email: c.mccabe@sheffield.ac.uk

PAC-Man Study — economic evaluation

The PAC-Man Study is a multi-centre, randomised controlled trial to evaluate the clinical and cost effectiveness of pulmonary artery catheters in patient management in intensive care. The Study is funded by the NHS R&D Health Technology Assessment Programme.

These days an economic evaluation has to form part of any randomised controlled trial. For PAC-Man, we need to do a detailed assessment of the costs of critical care in order to undertake this economic evaluation. Given that there is no validated "short method" currently available, we opted for data collection at the unit level rather than at the patient level, as we thought the latter would be an enormous burden on units. We are not using the Cost Block method, as it has never been externally validated, however, a bonus of our approach is the possibility of undertaking a validation of the Cost Block method.

What's in it for my unit?

The economic evaluation will also provide extremely valuable information on the cost and resource structure of your unit. Your cost data will be fed back to you with comparative data from other units* and should inform discussion on unit resources within your Trust by identifying the key cost drivers and the degree of variation between you and other units.

What's in it for critical care?

Not only will this research estimate the cost effectiveness of pulmonary artery catheters, it will also validate and inform further development of a "short method" for the economic evaluation of critical care.

So, why do we need a validated costing method for critical care? As you are aware, the NHS has become increasingly interested in identifying improvements in the population's health that results from its activities. The reason for this interest is that resources are (and always will be) limited, and therefore, it is important to maximise the health the NHS creates within its limited budget. For better or for worse, this objective has been formalised through the creation of the National Institute of Clinical Excellence (NICE) with its commitment to consider whether the NHS should provide therapies based primarily, although not exclusively, upon how cost effective those therapies are. The cost effectiveness of therapies measures how much health (normally measured in years of life or Quality Adjusted Life Years - QALYs) a therapy produces for each pound of resource spent.

What we don't want is a costing method imposed upon us from above...

The PAC-Man economic evaluation team, based in Sheffield, has extensive experience of supporting units in the collection of this type of resource and cost data. If your unit is finding it difficult, why not phone us and see if we can make it easier for you:

Chris McCabe
tel 0114 222 0728
(e-mail: c.mccabe@sheffield.ac.uk)

Katherine Stevens
tel 0114 222 0841
(e-mail: k.stevens@sheffield.ac.uk)

***Please be assured that all data provided will remain strictly confidential**

Notes and guidance for completion

'Your unit' is the unit participating in the PAC-Man Study, i.e. the facility within which intensive care is provided. If both high dependency and intensive care are provided within the same facility, then give the costs for both. Where high dependency is provided as a separate facility, please give the costs for your unit ONLY.

All information provided will be strictly confidential and no data will be published which will allow individual units to be identified.

We will provide you with feedback of how your unit compares with other units of a similar type, but these results will only be given to you and the other units will not be identified.

The questionnaire should be completed by relevant staff and returned directly to us in the pre-addressed envelope provided.

Please give information for the financial year 2002/03, i.e. 1 April 2002 to 31 March 2003.

You should include all equipment located within your unit. We have left blank rows for you to add any equipment that is in your unit but not covered by our list, or if there is not enough room under the headings. If you do not have an item please put '0' rather than leaving the cell blank.

If, for any reason, the year 2002/03 is significantly atypical, please explain why, but do not modify the numbers. If you have any questions, please do not hesitate to contact us.

Please print your answers clearly

Thank you very much for taking the time to complete this questionnaire

Please return (in the envelope provided) to:

Ms Katherine Stevens
Sheffield Health Economics Group
School of Health and Related Research
The University of Sheffield
Regent Court
30 Regent Street
Sheffield
S1 4DA

1. Cardiovascular/monitoring

	1	2	3	4	5	6
Item	**Total quantity**	**Model**	**Supplier**	**Age (years)**	**Is this equipment shared with other units or departments? (Y/N)**	**If yes, what proportion of time do you use it? (%)**
Patient monitors						
Type:						
Type:						
Type:						
Type:						
Portable/transfer monitors						
Type:						
Type:						
Type:						
Single parameter module:						
Multi parameter module:						
Other monitoring modules						
Type:						
Central processing unit:						
Portable non-invasive blood pressure machine:						
Oxygen saturation monitor:						
Bedside glucose analyser:						
12 Lead ECG recorder:						
ICP monitor:						
Blood gas analyser:						

Cont'd

1. Cardiovascular/monitoring *(cont'd)*

	1	2	3	4	5	6
Item	**Total quantity**	**Model**	**Supplier**	**Age (years)**	**Is this equipment shared with other units or departments? (Y/N)**	**If yes, what proportion of time do you use it? (%)**
Other near patient blood analyser						
Type:						
Tympanic thermometer:						
Other thermometers						
Type:						
Type:						
Defibrillator						
External pacemaker:						
Cardiac ECHO machine:						
Pulmonary artery catheter monitor:						
Ultrasonic vessel locator:						
Intra-aortic balloon pump device:						
Extra corporeal circulation machine:						
Trans-thoracic Doppler cardiac output monitor:						
Transoesophageal Doppler cardiac output monitor:						
Bioimpedance cardiac output device:						
PiCCO:						
Lidco:						

Cont'd

1. Cardiovascular/monitoring *(cont'd)*

	1	2	3	4	5	6
Item	**Total quantity**	**Model**	**Supplier**	**Age (years)**	**Is this equipment shared with other units or departments? (Y/N)**	**If yes, what proportion of time do you use it? (%)**
Please use this space to add any items in this section not already covered						

Person completing form:

Name (PRINT): Signature:

Date: / / (dd/mm/yyyy)

2. Respiratory

	1	2	3	4	5	6
Item	**Total quantity**	**Model**	**Supplier**	**Age (years)**	**Is this equipment shared with other units or departments? (Y/N)**	**If yes, what proportion of time do you use it? (%)**
Humidifier						
Type:						
Type:						
Type:						
Suction unit:						
Portable suction machine:						
Oxygen flow meter:						
CPAP unit:						
Portable oxygen unit:						
Non-invasive ventilator:						
Bipap machine:						
X-ray viewer:						
Ventilator						
Type:						
Type:						
Type:						
Type:						
Type:						

Cont'd

2. Respiratory *(cont'd)*

	1	2	3	4	5	6
Item	**Total quantity**	**Model**	**Supplier**	**Age (years)**	**Is this equipment shared with other units or departments? (Y/N)**	**If yes, what proportion of time do you use it? (%)**
Portable ventilator						
Type:						
Type:						
Type:						
Anaesthetic machine:						
Nitric oxide delivery system:						
Non disposable bag valve mask:						
Other gas flow meters:						
Entonox system:						
Gas scavenging system:						
Metabolic monitor:						
Gas monitoring equipment:						
Laryngoscope:						
Please use this space to add any items in this section not already covered						

Person completing form:

Name (PRINT): Signature:

Date: / / (dd/mm/yyyy)

3. Renal

	1	2	3	4	5	6
Item	**Total quantity**	**Model**	**Supplier**	**Age (years)**	**Is this equipment shared with other units or departments? (Y/N)**	**If yes, what proportion of time do you use it? (%)**
Haemofiltration machine						
Type:						
Type:						
Haemodialysis machine						
Type:						
Type:						
Water purifier (for dialysis):						
Activated clotting time machine:						
Please use this space to add any items in this section not already covered						

Person completing form:

Name (PRINT): Signature:

Date: / / (dd/mm/yyyy)

4. IV/Nutrition

	1	2	3	4	5	6
Item	**Total quantity**	**Model**	**Supplier**	**Age (years)**	**Is this equipment shared with other units or departments? (Y/N)**	**If yes, what proportion of time do you use it? (%)**
Volumetric pumps						
Type:						
Type:						
Type:						
Syringe pumps						
Type:						
Type:						
Type:						
PCA pump						
Type:						
Type:						
Type:						
Enteral nutrition pump						
Type:						
Type:						
Type:						
Pressure infusion devices						
Type:						
Type:						
Type:						

Cont'd

4. IV/Nutrition *(cont'd)*

	1	2	3	4	5	6
Item	**Total quantity**	**Model**	**Supplier**	**Age (years)**	**Is this equipment shared with other units or departments? (Y/N)**	**If yes, what proportion of time do you use it? (%)**
Epidural pump						
Type:						
Type:						
Type:						
Please use this space to add any items in this section not already covered						

Person completing form:

Name (PRINT): Signature:

Date: / / (dd/mm/yyyy)

5. General patient care

	1	2	3	4	5	6
Item	**Total quantity**	**Model**	**Supplier**	**Age (years)**	**Is this equipment shared with other units or departments? (Y/N)**	**If yes, what proportion of time do you use it? (%)**
Hoist:						
Bed frame						
Type:						
Type:						
Mattress						
Type:						
Type:						
Type:						
Therapy or low loss air beds						
Type:						
Type:						
Type:						
Drip stand:						
Patient bedside table:						
Patients chairs:						
Nurse bedside trolley (for charts etc.):						
Nurses' chair:						
Electric fan:						
Patient warmer i.e. bair hugger:						
Patient cooling system:						

Cont'd

5. General patient care *(cont'd)*

	1	2	3	4	5	6
Item	**Total quantity**	**Model**	**Supplier**	**Age (years)**	**Is this equipment shared with other units or departments? (Y/N)**	**If yes, what proportion of time do you use it? (%)**
Thromboembolic prevention devices eg. foot or leg pumps:						
Patient or bed scales:						
Any moving/handling equipment						
Type:						
Type:						
Type:						
Type:						
Please use this space to add any items in this section not already covered						

Person completing form:

Name (PRINT): Signature:

Date: / / (dd/mm/yyyy)

6. Diagnostics

	1	2	3	4	5	6
Item	**Total quantity**	**Model**	**Supplier**	**Age (years)**	**Is this equipment shared with other units or departments? (Y/N)**	**If yes, what proportion of time do you use it? (%)**
Gastroscope:						
Bronchoscope:						
Endoscope:						
Other Fibrescope:						
Fibrescope camera:						
Fibrescope monitor:						
Fibrescope light source:						
Fibrescope disinfection unit:						
Ophthalmoscope:						
Otoscope/auroscope:						
Please use this space to add any items in this section not already covered						

Person completing form:

Name (PRINT): Signature:

Date: / / (dd/mm/yyyy)

7. Other

	1	2	3	4	5	6
Item	**Total quantity**	**Model**	**Supplier**	**Age (years)**	**Is this equipment shared with other units or departments? (Y/N)**	**If yes, what proportion of time do you use it? (%)**
Blood warmer:						
Security camera:						
Washing machine:						
Dryer:						
Drugs fridge:						
Drugs freezer:						
Angle lamp:						
Trolley:						
Television:						
Music system/radio:						
Air conditioning unit:						
Ice maker:						
Water cooler:						
Patient transfer trolley:						
Video:						
Computerised information system workstation:						
Computerised information system central processing unit:						
Beam or pendant system:						
Please use this space to add any items in this section not already covered						

Person completing form:

Name (PRINT): Signature:

Date: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy)

8. Information technology/office

	1	2	3	4	5	6
Item	**Total quantity**	**Model**	**Supplier**	**Age (years)**	**Is this equipment shared with other units or departments? (Y/N)**	**If yes, what proportion of time do you use it? (%)**
Computer						
Type:						
Type:						
Type:						
Type:						
Printer						
Type:						
Type:						
Scanner:						
Camera						
Type:						
Type:						
Fax machine:						
Visitors chairs:						
Photocopier:						
Digital projector:						
Please use this space to add any items in this section not already covered						

Person completing form:

Name (PRINT): Signature:

Date: / / (dd/mm/yyyy)

9. Maintenance

Maintenance services are normally provided either by medical technicians employed by the hospital or covered by a maintenance contract. For equipment maintained under contract please give the annual cost (for 2002/03) of any maintenance contracts you have for the equipment in the unit. Please enter N/A if not applicable.

If the maintenance of your equipment is provided by medical technicians employed by the hospital, **and** they have **not** been included in your Staff Questionnaire, please give details below. If you are unsure, please call us on the telephone numbers given at the front of this booklet. Please enter N/A if not applicable.

Person completing form:

Name (PRINT): Signature:

Date: / / (dd/mm/yyyy)

PACMan

Pulmonary Artery Catheters in Patient Management

DIRECT PATIENT SUPPORT & OTHER MEDICAL AND SURGICAL SERVICES QUESTIONNAIRE

This questionnaire asks about direct patient support and other medical and surgical services for your unit for the financial year 2002/03 (1 April 2002 to 31 March 2003)

Centre Number: _____

Hospital Name: _____

Unit type: *(please tick (✓) appropriate)*

☐ ICU ☐ ICU/HDU

☐ ICU/CCU ☐ ICU/HDU/CCU

☐ Other (describe) _____

If you have any queries, please contact:

Ms Katherine Stevens Tel: 0114 2220841 email: k.stevens@sheffield.ac.uk
or Mr Chris McCabe Tel: 0114 2220728 email: c.mccabe@sheffield.ac.uk

PAC/CQ2/1/203

Direct patient support

1. Please give 2002/03 costs for:

Drugs, parenteral nutrition and intravenous fluid	£ _____ pa
Special feeds and catering	£ _____ pa
Medical gases	£ _____ pa
Imaging, including radiology and nuclear medicine – include charges for hospital x-rays and non staff running costs for unit based equipment (excl. depreciation)	£ _____ pa
Medical and surgical supplies	£ _____ pa
Dressings	£ _____ pa
Disposable linen	£ _____ pa
Linen	£ _____ pa
Patients' clothing	£ _____ pa
Staff uniforms	£ _____ pa
Provisions	£ _____ pa

2. ***EITHER***: Total pathology £ _____ pa

OR: Microbiology/virology £ _____ pa

Biochemistry £ _____ pa

Haematology, including blood products and cross-matching £ _____ pa

Histopathology (including post-mortem data) £ _____ pa

Other pathology (including cytogenetics) £ _____ pa

Cont'd...

Direct patient support *cont'd*

3. Please give 2002/03 costs for:

CSSD/TSSU	£ _____ pa
Dialysis fluids	£ _____ pa
Cleaning agents, fluids etc	£ _____ pa

If these items have already been included in costs listed in questions 1 and 2, please give details in the space below or enter N/A if not applicable.

_____

_____

_____

_____

_____

_____

_____

4. Please list any other patient services for which the unit **is charged**, and the total cost for 2002/03, for example physiotherapy. Please enter N/A if not applicable

Service	Total cost
_____	£ _____ pa
_____	£ _____ pa
_____	£ _____ pa
_____	£ _____ pa
_____	£ _____ pa
_____	£ _____ pa
_____	£ _____ pa
_____	£ _____ pa

Person completing form:

Name (PRINT): _____ Signature: _____

Date: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy)

Other medical and surgical services not covered in the budget

1. Please list any medical and surgical services (e.g. cardiologists) supplied to the unit, but **not** charged to the unit for the financial year 2002/03. Please indicate how often these services were provided during the year. Please enter N/A if not applicable.

Description	How often

2. Have any out-of-hours services been provided to the unit? Yes ☐ No ☐

   If **Yes**, please list them and how often they were provided during the year 2002/03 if they have not been included elsewhere.

Description	How often

Person completing form:

Name (PRINT): Signature:

Date: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy)

PACMan

Pulmonary Artery Catheters in Patient Management

STAFF QUESTIONNAIRE

This questionnaire asks for the salary employment costs for the staff attributed to your unit for the financial year 2002/03 (1 April 2002 to 31 March 2003)

Centre Number: _____

Hospital Name: _____

Unit type: *(please tick (✓) appropriate)*

☐ ICU ☐ ICU/HDU

☐ ICU/CCU ☐ ICU/HDU/CCU

☐ Other (describe) _____

If you have any queries, please contact:

Ms Katherine Stevens Tel: 0114 2220841 email: k.stevens@sheffield.ac.uk
or Mr Chris McCabe Tel: 0114 2220728 email: c.mccabe@sheffield.ac.uk

Medical staff costs

Please complete for **all** medical staff that have sessions (including on-call) in your unit during the financial year 2002/2003, excluding locum staff.

Medical Post	% WTE dedicated to the unit	Annual Salary of 1 WTE	Total Employment Cost*

WTE= Whole Time Equivalent Total Employment Costs – please calculate the total employment cost as the pro-rata salary cost for each post you list, including on-costs for each post.

Person completing form:

Name (PRINT): Signature:

Date: / / (dd/mm/yyyy)

Nursing staff costs

Please complete for **all** nursing staff working in your unit during the financial year 2002/03, **excluding** agency and bank staff.

Nurse Post	Grade (As grades A to I)	% WTE dedicated to the unit	Salary	Total Employment Cost*

WTE= Whole Time Equivalent Total Employment Costs – please calculate the total employment cost as the pro-rata salary cost for each post you list, including on-costs for each post.

Person completing form:

Name (PRINT): Signature:

Date: / / (dd/mm/yyyy)

Nursing staff costs
(continued)

Nurse Post	Grade (As grades A to I)	% WTE dedicated to the unit	Salary	Total Employment Cost*

WTE= Whole Time Equivalent Total Employment Costs – please calculate the total employment cost as the pro-rata salary cost for each post you list, including on-costs for each post.

Person completing form:

Name (PRINT): Signature:

Date: / / (dd/mm/yyyy)

Technical staff costs

Please complete for **all** technical staff working in your unit during the financial year 2002/2003, **excluding** agency and locum staff.

Name of Post	Grade	% WTE dedicated to the unit	Salary	Total Employment Cost*

WTE= Whole Time Equivalent Total Employment Costs – please calculate the total employment cost as the pro-rata salary cost for each post you list, including on-costs for each post.

Person completing form:

Name (PRINT): Signature:

Date: / / (dd/mm/yyyy)

Other clinical staff costs

Please complete for **all** other clinical staff working in your unit during the financial year 2002/03. This should include anyone that has sessions in your unit e.g. physiotherapists, dieticians, pharmacists etc.

Name of Post	Grade	% WTE dedicated to the unit	Salary	Total Employment Cost*

WTE= Whole Time Equivalent Total Employment Costs – please calculate the total employment cost as the pro-rata salary cost for each post you list, including on-costs for each post.

Person completing form:

Name (PRINT): Signature:

Date: / / (dd/mm/yyyy)

Non-clinical managerial and administrative staff costs

Please complete for **all** non-clinical managerial and administrative staff working in your unit during the financial year 2002/2003, **excluding** agency and temporary staff. **Include** secretarial and reception staff, audit clerks etc.

Name of Post	Grade	% WTE dedicated to the unit	Salary	Total Employment Cost*

WTE= Whole Time Equivalent Total Employment Costs – please calculate the total employment cost as the pro-rata salary cost for each post you list, including on-costs for each post.

Person completing form:

Name (PRINT): Signature:

Date: / / (dd/mm/yyyy)

Other staff costs

If there are any other staff costs incurred by your unit that have not already been covered in the previous categories, please give details below.

Name of Post	Grade	% WTE dedicated to the unit	Salary	Total Employment Cost*

WTE= Whole Time Equivalent Total Employment Costs – please calculate the total employment cost as the pro-rata salary cost for each post you list, including on-costs for each post.

Person completing form:

Name (PRINT): Signature:

Date: / / (dd/mm/yyyy)

Thank you for your help

Please return the completed questionnaire in the envelope supplied

PACMan

Pulmonary Artery Catheters in Patient Management

UNIT CHARACTERISTICS, SUPPORT SERVICES AND WORKS QUESTIONNAIRE

This questionnaire asks about characteristics, support services and works for your unit for the financial year 2002/03 (1 April 2002 to 31 March 2003

Centre Number: ☐

Hospital Name: ☐

Unit type: *(please tick (✓) appropriate)*

☐ ICU ☐ ICU/HDU

☐ ICU/CCU ☐ ICU/HDU/CCU

☐ Other (describe) ☐

If you have any queries, please contact:

Ms Katherine Stevens Tel: 0114 2220841 email: k.stevens@sheffield.ac.uk
or Mr Chris McCabe Tel: 0114 2220728 email: c.mccabe@sheffield.ac.uk

Unit Characteristics

All questions are for the financial year 2002-200

1. Is the unit a purpose-built building? **YES** ☐ **NO** ☐
   (i.e. was the facility built with the intention of housing an ICU)

2. Approximately how long is it since the building housing the unit was constructed or had a major refurbishment? **YEARS** ☐

3. Was the building housing the unit designed for a limited period of life? **YES** ☐ **NO** ☐

   If **Yes**, what was its design life? **YEARS** ☐

4. Is any major structural work planned for the unit in the next 12 months? **YES** ☐ **NO** ☐
   If **Yes**, please give details

_____

_____

_____

_____

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_____

_____

_____

Person completing form:

Name (PRINT): ☐ Signature: ☐

Date: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy)

Instructions for the following section

Does your unit (please tick (✓) **one** box **only**)**:**

1. have ICU beds (level 3) **only**, i.e. there are **no** designated high dependency beds? ☐

   Please complete **Part A** for your ICU beds

2. have a policy of using beds flexibly, i.e. a variable ratio of ICU and high dependency beds? ☐

   Please complete **Part A** for your ICU beds and high dependency beds

3. have designated ICU beds (level 3), used for ICU patients only, **and** designated high dependency beds, used for high dependency patients only? ☐

   Please complete **Part A** for your ICU beds and **Part B** for your high dependency beds

PART A
Intensive care

1. How many beds are funded for your unit for the year 2002/03? ☐☐☐

2. What is the total number of beds in your unit for the year 2002/03? (i.e. that 'physically exist') ☐☐☐

3. What is the total number of available beds in your unit for the year 2002/03? (i.e. that can be used) ☐☐☐

4. Where bed availability is less than the total beds in your unit (Question 2), please give reasons for this below or enter N/A if not applicable.

_____

_____

_____

5. What was the total occupancy* in your unit for the year 2002/03? ☐☐☐

PART B
High Dependency

6. How many beds are funded for your unit for the year 2002/03? ☐☐☐

7. What is the total number of beds in your unit for the year 2002/03? (i.e. that 'physically exist') ☐☐☐

8. What is the total number of available beds in your unit for the year 2002/03? (i.e. that can be used) ☐☐☐

9. Where bed availability is less than the total beds in your unit (Question 7), please give reasons for this below or enter N/A if not applicable.

_____

_____

_____

10. What was the total occupancy* in your unit for the year 2002/03? ☐☐☐

*** Please give the mean and standard deviation of the daily proportions of the total beds occupied at 00.00 hours (midnight) each day relative to the total number of beds available**

Person completing form:

Name (PRINT): _____ Signature: _____

Date: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy)

PLEASE COMPLETE **EACH** QUESTION

Support Services and Works

Please give as accurately as possible

11. What is the floor area of the unit ☐☐☐ m^2

12. What is the heated volume of the unit? ☐☐☐ m^3

13. What is the cost of heat, light and power (including hot water)?
(If necessary, apportion on the basis of the volume of the unit as a percentage of total hospital volume. If you prefer, give the total cost of heat, light and power.)

    Electricity £ _____ pa

    Coal/Oil/Gas £ _____ pa

    OR

    Total heat, light and power £ _____ pa

14. What are the 2002/03 building maintenance costs for the unit?
(If necessary, apportion on the basis of the volume of the unit as a percentage of total hospital volume) £ _____ pa

15. What are the local authority rates for 2002/03 and other utility charges?
(If necessary apportion on the basis of the volume of the unit as a percentage of total hospital volume)

    General rates £ _____ pa

    Water/Sewerage rates £ _____ pa

16. What are the support service costs for the unit for 2002/03 for:

    Portering *(if necessary, use bed occupancy to apportion)* £ _____ pa

    Cleaning *(if necessary, use area cleaned to apportion)* £ _____ pa

    Laundry *(if necessary, use number of pieces to apportion)* £ _____ pa

    Hospital administration *(if necessary, use bed occupancy to apportion)* £ _____ pa

    Postage and/or telephone *(if separate from administration)* £ _____ pa

    Medical records *(if necessary, use bed occupancy to apportion)* £ _____ pa

    Transport *(excluding ambulance service)* £ _____ pa

17. If ambulance transport for the unit is paid for by the hospital, please give the cost for 2002/03 £ _____ pa

    If **not**, please give an estimate of the number of patients arriving at the unit by ambulance in 2002/03 ☐☐☐☐ patients

Person completing form:

Name (PRINT): _____ Signature: _____

Date: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy)

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HTA Commissioning Board

Members

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Current and past membership details of all HTA 'committees' are available from the HTA website (www.hta.ac.uk)

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Research Degrees Programme Director & Reader in Psychology, Health Services Research Unit, London School of Hygiene and Tropical Medicine, London

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Consumer member, HTA – Expert Advisory Network

Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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