Post-Intensive Care Risk-adjusted Alerting and Monitoring (PICRAM) study. Phase 1

Ethics reference: 11\SC\0440

Funder's reference: HICF-0510-006

20/09/2011 : Version 1.1

Lead Investigator and Contact:	Dr Duncan Young Adult Intensive Care Unit John Radcliffe Hospital Headley Way Headington Oxford OX3 9DU
Investigators:	Prof Lionel Tarassenko Institute of Biomedical Engineering ORCRB Old Road Campus off Roosevelt Drive Headington Oxford OX3 7DQ
	Dr Peter Watkinson Adult Intensive Care Unit John Radcliffe Hospital Headley Way Headington Oxford OX3 9DU
Sponsor:	University of Oxford
Funder:	Health Innovation Challenge Fund, Department of Health and Wellcome Trust.

Signatures:

Dr J D Young Date

AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	1.1	20/09/2011	Julie Darbyshire	Ethics ref added

1. SYNOPSIS

Study Title	Post-Intensive Care Risk-adjusted Alerting and Monitoring (PICRAM) study. Phase 1.
Study Design	Algorithm development from linked clinical databases
Study Data Source	Data from patients discharged alive from adult general intensive care units in Oxford and Reading
Planned Sample Size	2000 records
Planned Study Period	12 months
Primary Objective	To develop two mathematical models. The first model will link physiological and demographic variables recorded during an individual patient's ICU (intensive care unit) stay with their risk of death following ICU discharge. The second will determine the probability that physiological variables recorded in the last three days of a patient's stay are "normal" for that patient group.
Secondary Objectives	This is the first phase of a two part study and will develop and validate the mathematical models. The second phase of the study will use these models to adjust the alarm thresholds built into a "wearable", telemetry based physiological monitoring system. The second phase will have a separate protocol and ethics approval.
Intervention (s)	No intervention

2. BACKGROUND AND RATIONALE

Background and rationale for Phase 1 of the PICRAM study

Unmet healthcare need.

The 240 UK ICUs admit about 110,000 patients annually. Data on admissions to 185 ICUs in 2006-8 (ICNARC, Intensive Care Audit and Research Centre database) revealed that 77% of patients were discharged to the ward recovering from their acute illness, but 11% then died before leaving hospital. Most deaths occurred without readmission to the ICU, suggesting that physiological changes preceding agonal events went unrecognised and so treatment to prevent the patient's demise could not be delivered. Failure to recognise and act on physiological indicators of worsening acute illness in acute hospital wards is a generic problem that was recognised over a decade ago [1] and which prompted the NICE clinical guidelines number 50 (2007) [2]. These guidelines recommend "Track and Trigger" physiological scoring systems, coupled with a graded response including critical care outreach services (CCOSs). In spite of NICE endorsement and widespread adoption, limited evaluation shows these systems have low sensitivity and positive predictive values, albeit with high specificity [3, 4]. Research commissioned by the National Institute for Health Research Service Delivery and Organisation (NIHR SDO) [5] showed that neither the implementation of "Track and Trigger" systems nor the commissioning of CCOSs per se influenced post-ICU mortality. Post-ICU patients who were regularly reviewed by any member of the ICU team did however derive a survival benefit, but ICUs were very rarely resourced for this, especially outside office hours. Thus there is an unmet need for a far more effective recognition/response system for acutely unwell patients generally, and a specific need for patients discharged from ICU, who after an expensive and traumatic period of treatment still experience a high in-hospital mortality, amounting to over 9000 deaths annually in the UK, some of which are demonstrably avoidable.

The PICRAM project overall will use risk-prediction models applied to data collected during a patient's ICU stay to adjust the alarm thresholds built into a "wearable", telemetry based physiological monitoring system attached tothe patients after ICU discharge.

Importance of the proposed work.

Deaths in patients discharged alive from ICUs represent about four times the annual road traffic fatalities in the UK. These patients are part of a larger group of acutely unwell and deteriorating patients in hospital heavily targeted by policy makers over the last decade [6-8]. In the current economic climate relatively expensive services above and beyond core healthcare provision, such as CCOSs and follow up of post-ICU patients on the ward, are at risk and more economical solutions are needed.

Overview of existing technologies.

There are no scoring systems available that estimate the risk of post-ICU death or deterioration at the point of discharge from the ICU. The systems available at present all rely solely on detecting impending problems from changes in vital signs after ICU discharge. The simplest technology to detect deterioration in patients after discharge from an ICU is a paper "Track and Trigger" form onto which vital signs are recorded. Each vital sign is turned into a

numeric score, and the sum of the scores determines whether further action is needed. This system is very liable to human error, especially in busy, understaffed wards The scoring systems (Early Warning Scores) used on both paper and paperless systems to convert vital signs to a single linear scale for simple alerting are all empirical with unknown measurement properties.

Work/analyses undertaken on existing data

We have already produced an equation to estimate the probability of a patient dying in hospital after ICU discharge using data held by ICNARC on 198,000 admissions to 185 UK ICUs. This model is limited by the dataset we used to derive it, which only contains information about the patient during the first 24 hours of admission to an ICU, as it is primarily used for case-mix adjustment and comparative audit. To overcome this limitation we will construct a two mathematical models to estimate the probability of post-ICU death from detailed datasets covering the whole ICU stay which are available for about 8000 admissions over the last 13 years in Oxford and 3000 admissions over 6 years in Reading, recorded on the Clinical Information Systems (CIS). Techniques have been developed during other studies [eg. 9] to extract, clean and validate data of interest from these databases. The databases held on the CIS's contain a large number of variables, so some selection will be needed prior to modelling. We will do this using a systematic review of the literature on the prediction of post ICU mortality (completed) and expert panels (part of this workstream).

These risk predictions will be used in phase 2 of the study to customise a continuous monitoring/alerting system to provide patient-specific alerts, so high-risk patients have lower alerting thresholds.

3. OBJECTIVE

To develop two mathematical models. The first model will link physiological and demographic variables recorded during an individual patient's ICU (intensive care unit) stay with their risk of death following ICU discharge. The second will determine the probability that physiological variables recorded in the last three days of a patient's stay are "normal" for that patient group.

4. STUDY DESIGN

A retrospective linked database study using three different sets of clinical databases.

Data sources:

Database set 1: Phillips ICIP (CareVue) databases used to record demographics, clinical data and treatment of critically ill patients in the John Radcliffe and Churchill Hospitals (one common database) in Oxford, and the Royal Berkshire Hospital in Reading.

Database set 2: ICNARC (Intensive Care National Audit and Research Centre) databases in the John Radcliffe and Churchill Hospitals (one common database) in Oxford, and the Royal

Berkshire Hospital used for audit purposes containing details of in-hospital deaths of patients who have been treated on the ICUs in these hospitals.

Database set 3: The PAS (Patient Administration System) databases or their Electronic Patient Record successors in the John Radcliffe and Churchill Hospitals (one common database) in Oxford, and the Royal Berkshire Hospital for verification of in-hospital deaths of patients who have been treated on the ICUs in these hospitals.

Study sequence following Ethics and NIGB approval:

1) Identification of candidate variables in the Phillips ICIP databases likely to be associated with in-hospital deaths of patients who have been treated on the ICUs using literature searches and unpublished results from our previous work.

2) Identification of candidate variables in the Phillips ICIP databases likely to be associated with in-hospital deaths of patients who have been treated on the ICUs using expert panel techniques.

3) Deciding feature extraction techniques to select which variables or derivatives to use for modelling from those that are that are repeatedly represented in a patient's ICU record (for example blood pressure, temperature etc).

4) Extraction of these variables and derivatives from the main (clinical) Phillips ICIP database in Oxford only for all patients surviving their ICU stay in the last 5 years and creation of a study database.

5) Extraction of vital status at hospital discharge for all patients surviving their ICU stay in the last 5 years identified in (4) from the main (clinical) ICNARC database in Oxford only and addition of these data to the study database.

6) Extraction of vital status at hospital discharge from the PAS database for patients surviving their ICU stay in the last 5 years identified in (4) for whom vital status at hospital discharge is not available from the main (clinical) ICNARC database in Oxford and addition of these data to the study database.

7) Verification of the ICNARC vital status record against the PAS vital status record for a randomly-selected sample of 200 patients in Oxford.

8) Anonymisation of the study database after validity checks.

9) Development of a logistic regression model using standard techniques with the variables developed in (4) as the explanatory variables and the vital status at hospital discharge as the dependent variable.

10) Assessment of the feasibility of developing a Cox regression (survival) model using standard techniques with the variables developed in (4) as the explanatory variables and the time to in-hospital death as the dependent variable.

11) Using the study database, a computer model of 'normality' for five vital signs (blood pressure, heart rate, arterial oxygen saturation, respiratory rate, temperature) modelled over time for the last three days of surviving patients' ICU stay, or the whole stay if shorter, will be developed using the equivalent of a six-dimensional histogram. A standard, one-dimensional, histogram is effectively a probability distribution, or density, estimate for that variable. In six dimensions, the probability density can be estimated using data fusion or pattern recognition techniques, such as Parzen windows. This will give a time series of estimates of the probability that these data are normal for an ICU patient at the end of their stay.

12) Extraction of variables and derivatives used in the regression model from the main (clinical) Phillips ICIP database in Reading only for all patients surviving their ICU stay in the last 2 years and creation of a test database.

13) Extraction of vital status at hospital discharge for all patients surviving their ICU stay in the last 2 years identified in (11) from the main (clinical) ICNARC database in Reading only and addition of these data to the test database.

14) Extraction of vital status at hospital discharge from the PAS database for patients surviving their ICU stay in the last 2 years identified in (11) for whom vital status at hospital discharge is not available from the main (clinical) ICNARC database in Reading and addition of these data to the test database.

15) Verification of the ICNARC vital status record against the PAS vital status record for a randomly-selected sample of 200 patients in Reading.

16) Anonymisation of the test database after validity checks.

17) Testing of the generalisability of the logistic regression model developed in (9) (and if appropriate the Cox regression model developed in (10)) on the test data set from Reading using calibration curves, the Hosmer–Lemeshow test for goodness of fit and other techniques.

18) Application of the computer model of normality (see 11) to the test database from Reading generated at step (11) and confirmation that the distribution of probabilities matches the Oxford distribution.

At this point the models required for the clinical phase of the study will have been developed and tested. Regulatory approval for Phase 2 will then be sought.

5. Interventions

There are no interventions.

6. SAFETY reporting

N/A.

7. Ethics, Confidential Data Handling

Handling of patient-identifiable information and other information in the study.

Database linkage studies require each patient to be uniquely identifiable in each database. The linking fields usually comprise hospital number, NHS number, date of birth, postcode and name. Thus until the study database is created and anonymised we will be accessing patient information without their knowledge. This will require NIGB approval.

To maximise patient confidentiality all identifiable data will be kept on servers under the control of the two Trusts involved (Oxford Radcliffe Hospitals NHS Trust and the Royal Berkshire NHS Foundation Trust), where the construction of the study database will take place. Once the data are merged from the three sources onto the study database at each site, each patient will be assigned a study number, the identifiers will be removed and the database anonymised. An identical process will be followed for the test database.

Once the study and test databases have been anonymised they will be moved onto the secure University of Oxford servers to allow the analysis/model development to proceed.

All study management data and electronic correspondence will be stored securely on Trust or University password-protected servers as appropriate only accessible by study staff and authorised personnel. Any paper correspondence will be kept in the Kadoorie Centre in the research area, behind two access-controlled doors and in locked filing cabinets.

The NIGB approval process will require detailed security assessments to be submitted.

The final database will be available for future research and access will be governed by the PICRAM Project Management Group. Specifically, a 'request to use data' form will be available and the PICRAM Project Management Group will review all requests to utilise the dataset collected as part of the PICRAM project. As part of the application process prospective researchers will need to demonstrate a clear research plan, with funding and an indication of analysis methods, and show that they have considered existing work in the field before access to the data is granted.

8. Financing and Insurance

The University of Oxford.

9. REFERENCES

1. McQuillan P, Pilkington S, Allan A, Taylor B, Short A, Morgan G, Nielsen M, Barrett D, Smith G, Collins CH. “Confidential inquiry into quality of care before admission to intensive care.”
BMJ 1998 316;1853-8.

2. NICE clinical guideline 50 “Acutely ill patients in hospital: recognition of and response to acute illness in adults in hospital” National Institute for Health and Clinical Excellence, London2007
3. Fletcher SJ, Cuthbertson BH. “Outreach, epistemology and the evolution of critical care.” Anaesthesia 2010 65;115-8.
4. Jansen JO, Cuthbertson BH. “Detecting critical illness outside the ICU: the role of track and trigger systems.” Curr Opin Crit Care 2010 Epub ahead of print
5. Project SDO/74/2004 “Evaluation of outreach services in critical care.” Service Delivery and Organisation (SDO), London 2007
6. “Comprehensive Critical Care. A review of adult critical care services.” Department of Health, London 2000
7. “The National Outreach Report,” Department of Health, London 2005
8. “An Acute Problem.” National Confidential Enquiry into Patient Outcome and Death (NCEPOD) London 2005
9. Bone EG, Young D, Chantler J.”Target ranges and the apparent compliance with tight glycaemic control.” Anaesthesia 2006 61;956–8
10. Watkinson PJ, Barber VS, Price JD, Hann A, Tarassenko L, Young JD. “A randomised controlled trial of the effect of continuous electronic physiological monitoring on the adverse event rate in high risk medical and surgical patients.” Anaesthesia 2006 61;1031–9
11. Hravnak M, Edwards L, Clontz A, Valenta C, DeVita MA, Pinsky MR. “Defining the incidence of cardiorespiratory instability in patients in step-down units using an electronic integrated monitoring system.”’ Arch Int Med 2008 168;1300–8