Evaluation of triage methods used to select patients with suspected pandemic influenza for hospital admission: cohort study

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Declared competing interests of authors: KC was one of the developers of the PMEWS score, evaluated in this report.

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Abstract

Evaluation of triage methods used to select patients with suspected pandemic influenza for hospital admission: cohort study

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Background: Triage methods are necessary in emergency departments to provide clinicians with a reliable method for determining each patient's risk of adverse outcome. Prior to the 2009 H1N1 influenza pandemic the CURB-65 (a risk prediction score for pneumonia, based on confusion, urea level, respiratory rate, blood pressure and age over 65 years) pneumonia score and the Pandemic Modified Early Warning Score (PMEWS) were used to assess adults. In response to the emergence of the pandemic, national guidance produced a new swine flu hospital pathway for use adults and children. However, none of these methods had been widely validated or tested in the setting of pandemic influenza.

Objectives: To use the initial waves of the 2009 H1N1 pandemic to evaluate existing triage methods in patients presenting with suspected pandemic influenza, and to determine whether an improved triage method could be developed.

Methods: A prospective cohort study was undertaken of patients with suspected swine flu presenting to four hospitals during the second wave of the 2009 H1N1 pandemic. Staff completed a standardised assessment form that included the CURB-65 score, PMEWS and the swine flu hospital pathway. Patients who died or required respiratory, cardiovascular or renal support during the 30-day follow-up were defined as having a poor outcome. Patients who survived to 30 days without requiring respiratory, cardiovascular or renal support were defined as having a good outcome.

Results: Data were collected and analysed from 481 cases across three hospitals. Most of the cases were children, with 347 out of 481 (72%) aged 16 years or less. There were five poor outcomes: two deaths and three survivors who required respiratory support. The five patients with poor outcomes had CURB-65 scores of zero, one (three cases) and two, and PMEWS scores of one, five, six, seven and eight. The swine flu hospital pathway was positive in three out of five cases. The *C*-statistic for each method was CURB-65 0.78 [95% confidence interval (CI) 0.58 to 0.99], PMEWS 0.77 (95% CI 0.55 to 0.99) and the swine flu hospital pathway 0.70 (95% CI 0.45 to 0.96). Patients with a higher CURB-65 score were more likely to be admitted ($p < 0.001$): 25 out of 101 (25%) with a score of zero, 11 out of 24 (46%) with a score of one, 7 out of 8 (88%) with a score of two, and the patient with a score of three were admitted. Admitted patients had a higher mean PMEWS score (4.6 vs 2.0, $p < 0.001$). The *C*-statistics for CURB-65, PMEWS and the swine flu hospital pathway in adults in terms of discriminating between those admitted and discharged were 0.65 (95% CI 0.54 to 0.76), 0.76 (95% CI 0.66 to 0.86) and 0.62 (95% CI 0.51 to 0.72) respectively.

Limitations: The 2009 H1N1 pandemic was much smaller and less severe than predicted and resulted in a lack of sufficient data.

Conclusions: Potential concerns were raised about the use of existing triage methods for patients with suspected pandemic influenza, as these methods may fail to discriminate between patients who will have an adverse outcome and those with a benign course. Clinicians in the study did not generally appear to admit or discharge on the basis of these methods, despite their recommended use. Further research is required to evaluate existing triage methods and develop new triage tools for suspected pandemic influenza.

Contents

List of abbreviations

AUROC	area under the receiver–operator characteristic curve (*C*-statistic): a measure of the discriminant value of a risk prediction score
CAF	Clinical Assessment Form
CAT	Community Assessment Tool: a decision pathway for determining which patients with suspected pandemic influenza require hospital assessment and admission; it forms the basis of the swine flu hospital pathway
CLRN	Comprehensive Local Research Network
CURB-65	A risk prediction score for pneumonia, based on confusion, urea level, respiratory rate, blood pressure and age over 65 years
ECC	Ethics and Confidentiality Committee: a subcommittee of the NIGB
ECG	electrocardiogram
GCS	Glasgow Coma Score
HPA	Health Protection Agency
ICNARC	Intensive Care National Audit and Research Network
IRAS	Integrated Research Application System
NIGB	National Information Governance Board
PMEWS	Pandemic Modified Early Warning Score: a risk score for pandemic influenza based on physiological variables, age, social factors, chronic disease and performance status
PMG	Project Management Group
REC	Research Ethics Committee
ROC	receiver-operator characteristic
SD	standard deviation
SLSP	System Level Security Policy
SSI	Site Specific Information

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

Executive summary

Background

The UK influenza pandemic contingency plan published in 2007 predicted around 750,000 excess emergency department attendances and 82,500 excess hospitalisations during a pandemic. Clinicians working in the emergency department need a rapid and reliable method for determining each patient's risk of adverse outcome. Prior to the emergence of the 2009 H1N1 pandemic, Health Protection Agency (HPA) guidance, supported by the British Thoracic Society and British Infection Society, recommended the use of the CURB-65 (a risk prediction score for pneumonia, based on confusion, urea level, respiratory rate, blood pressure and age over 65 years) pneumonia score for adults. Department of Health guidelines on surge capacity in a pandemic also considered use of a physiological–social score [Pandemic Modified Early Warning Score (PMEWS)] for adults. National guidance produced in response to the emergence of H1N1 influenza included a new swine flu hospital pathway for emergency department management with seven criteria based upon a Community Assessment Tool (CAT) for adults and children. These potential triage methods have not been widely validated and, in particular, have not been tested in the setting of pandemic influenza.

Objectives

We aimed to use the initial waves of the 2009 H1N1 pandemic to evaluate existing emergency department triage methods for predicting severe illness or death in patients presenting with suspected pandemic influenza, and to determine whether an improved triage method could be developed. Our specific objectives were to determine:

1. the discriminant value of the CURB-65 score, PMEWS and the swine flu hospital pathway for predicting severe illness or death in adults presenting with suspected pandemic influenza and the discriminant value of the swine flu hospital pathway for predicting severe illness or death in children
2. the independent predictive value of presenting clinical characteristics and routine tests for severe illness or death in patients presenting with suspected pandemic influenza
3. whether the discriminant value of emergency department triage can be improved by developing two new triage methods based upon (1) presenting clinical characteristics alone and (2) presenting clinical characteristics, electrocardiogram, chest radiograph and routine blood test results.

Methods

We undertook a prospective cohort study of patients presenting to the emergency department of four hospitals with suspected pandemic influenza during the second wave of the 2009 H1N1 pandemic. Emergency department staff identified patients with suspected pandemic influenza and then completed a standardised assessment form that included the elements of the CURB-65 score, PMEWS, the swine flu hospital pathway and any other measures that could be routinely recorded in the emergency department.

Outcome assessment was based on researcher review of hospital computer records and case notes. Patients who died or required respiratory, cardiovascular or renal support during the 30-day follow-up were defined as having a poor outcome. Patients who survived to 30 days without requiring respiratory, cardiovascular or renal support were defined as having a good outcome. We also recorded whether they were treated with antiviral agents or antibiotics, and the length and location of any hospital stay.

We planned to assess CURB-65, PMEWS and the swine flu clinical pathway by calculating the area under the receiver–operator characteristic curve (*C*-statistic) for discriminating between cases with and without a poor outcome. We also planned to use multivariable logistic regression to determine the independent predictive value of presenting clinical characteristics and routine tests and to develop two new triage scores: one based on initial assessment only and the other based on all emergency department data.

Results

The 2009 H1N1 pandemic was much smaller and less severe than predicted. Data were collected and analysed from 481 cases across three hospitals in the second wave of the pandemic. Most of the cases were children, with 347 out of 481 (72%) aged 16 years or less. There were only five poor outcomes according to our definition: two deaths and three survivors who required respiratory support. We therefore lacked sufficient data to determine the independent predictive value of presenting clinical characteristics and routine tests or develop any new triage methods.

The five patients with poor outcomes had CURB-65 scores of zero, one (three cases) and two, and PMEWS scores of one, five, six, seven and eight. The swine flu hospital pathway was positive in three out of five cases. The *C*-statistic for each method was CURB-65 0.78 [95% confidence interval (CI) 0.58 to 0.99], PMEWS 0.77 (0.55 to 0.99) and the swine flu hospital pathway 0.70 (0.45 to 0.96).

Patients with a higher CURB-65 score were more likely to be admitted ($p < 0.001$): 25 out of 101 (25%) with a score of zero, 11 out of 24 (46%) with a score of one, 7 out of 8 (88%) with a score of two, and the patient with a score of three were admitted. Admitted patients had a higher mean PMEWS score (4.6 vs 2.0, $p < 0.001$). The *C*-statistics for CURB-65, PMEWS and the swine flu hospital pathway in adults in terms of discriminating between those admitted and discharged were 0.65 (95% CI 0.54 to 0.76), 0.76 (95% CI 0.66 to 0.86) and 0.62 (95% CI 0.51 to 0.72) respectively.

Conclusions

We can draw no reliable conclusions from the data available other than raise potential concerns about the use of existing triage methods for patients with suspected pandemic influenza. Our very limited data suggest these methods may fail to discriminate between patients who will have an adverse outcome and those with a benign course. Furthermore, clinicians in our study did not generally appear to admit or discharge on the basis of these tools, despite being recommended for use in the pandemic.

Implications for practice

In the absence of evidence for the use of these triage tools, emergency department clinicians should continue to base triage decisions for patients with suspected pandemic influenza upon their clinical judgement.

Recommendations for research

Further research is required to evaluate existing triage tools and develop new triage methods for suspected pandemic influenza. This may require evaluation in surrogate conditions, such as pneumonia or seasonal influenza. Research is also required to determine the feasibility and acceptability to patients of undertaking research during a pandemic using confidential patient information without consent.

Chapter 1
Introduction

Influenza pandemics have occurred at least three times in the last century. Their severity ranges from similar to seasonal influenza to a major international threat to health, with millions becoming ill and a proportion dying. A pandemic thus has the potential to place a huge strain upon health services, particularly the emergency care services, which may be exacerbated by staff sickness absence due to influenza.

The timing, course and severity of a pandemic are difficult to predict, but estimates of the number of cases and the burden upon health services are necessary to assist planning. The UK influenza pandemic contingency plan published in 2007 predicted around 750,000 excess emergency department attendances and 82,500 excess hospitalisations during a pandemic.[1] Under these circumstances it would be impractical for all patients fully to be assessed by a senior clinician. We therefore need methods of triage and resource allocation that are fair, robust and reproducible.[2]

The term *triage* is often used to describe a brief initial assessment in the emergency department to determine patient order of priority in the queue to be seen. However, it can be used more broadly to include the full process of emergency assessment, including investigations such as blood tests and radiography, and can be applied to decision-making regarding whether the patient should be admitted to hospital and whether he/she should be referred for high-dependency or intensive care.

Emergency department triage methods need to accurately predict the individual patient's risk of death or severe illness. The predicted risk can then guide decision-making. Patients with a low risk may be discharged home, those with a high risk admitted to hospital, and those with a very high risk referred for high-dependency or intensive care. The level of risk used to trigger these decisions need not necessarily be fixed or determined in advance. Indeed, decision-making thresholds could change during the course of a pandemic as the balance between resource availability and demand changes. Triage methods that use a risk prediction score to determine the need for hospital care may therefore be more useful than a triage rule that classifies patients into admission and discharge categories.

In April 2009, a new strain of the A/H1N1 influenza virus (known as swine flu) was detected in Mexico and started to spread globally. In June, the World Health Organization declared the outbreak to be a pandemic. The virus spread to the UK, leading to a first wave of cases in July 2009 and a second wave in October and November 2009. The initial waves of the pandemic provided an opportunity to undertake research that could then guide patient management in subsequent waves or future pandemics.

Prior to the emergence of the 2009 H1N1 pandemic, Health Protection Agency (HPA) guidance, supported by the British Thoracic Society and British Infection Society, recommended the use of the CURB-65 pneumonia score[3] in adults, shown in Appendix 1. This score uses five variables (confusion, urea level, respiratory rate, blood pressure and age) to generate a score between zero and five. Department of Health guidelines on surge capacity in a pandemic also considered use of a physiological–social score [Pandemic Modified Early Warning Score (PMEWS)][4] for adults, shown in Appendix 2. This score uses physiological variables, age, social factors, chronic disease and performance status to generate a score between zero and 20. National guidance produced in response to the emergence of H1N1 influenza included a new swine flu hospital pathway for emergency department management with seven criteria. This was based upon a Community Assessment Tool (CAT) consisting of seven criteria, any one of which predicts increased risk and the need for hospital assessment[5] in adults and children. This is shown in Appendices 3 (adults) and 4 (children).

Existing literature shows CURB-65 to perform reasonably well as a mortality predictor in an emergency department population with community-acquired pneumonia {AUROC [area under the receiver–operator characteristic curve (*C*-statistic): a measure of the discriminant value of a risk prediction score] 0.76},[6] but less well in predicting the need for high-level care (AUROC

0.69[7] and 0.64[8]). The physiological–social score considered by the Department of Health (PMEWS) is not a particularly good predictor of death in community-acquired pneumonia (used as a proxy for pandemic influenza), with an AUROC score of 0.66, but performed much better when predicting a requirement for higher-level care (AUROC 0.83)[8] and has shown promise when used in the prehospital setting to determine need for emergency department attendance (AUROC 0.71[9] and 0.8[10]). The national guidelines produced for the H1N1 pandemic appear to have been developed by expert consensus without validation in the appropriate patient populations.

To our knowledge there have been no studies evaluating any of these triage methods in patients with suspected pandemic influenza, and no studies to develop a risk-prediction score in the emergency department population with suspected pandemic influenza. We therefore aimed to use the initial waves of the H1N1 pandemic to evaluate existing emergency department triage methods for predicting severe illness or death in patients presenting with suspected pandemic influenza, and determine whether an improved triage method could be developed.

Our specific objectives were to determine:

1. the discriminant value of the CURB-65 score, PMEWS and the swine flu hospital pathway for predicting severe illness or death in adults presenting with suspected pandemic influenza, and of the swine flu hospital pathway for predicting severe illness or death in children
2. the independent predictive value of presenting clinical characteristics and routine tests for severe illness or death in patients presenting with suspected pandemic influenza
3. whether the discriminant value of emergency department triage can be improved by developing two new triage methods based upon (1) presenting clinical characteristics alone and (2) presenting clinical characteristics, electrocardiogram (ECG), chest radiograph and routine blood test results.

The first new triage method would use only variables available at initial patient assessment, i.e. history and examination, including simple technologies such as automated blood pressure measurement and pulse oximetry. This triage method could be used to assess patients for the need for hospital investigation and identify patients that could be discharged without further assessment.

The second new triage method would be based upon all available emergency department data, including routine blood tests, ECG and chest radiograph findings. This triage method could be used for two potential purposes: (1) identification of patients with a low risk of adverse outcome, who can be discharged home after emergency department assessment, and (2) identification of high-risk patients who are likely to need high-dependency or intensive care.

Chapter 2
Methods

We undertook a prospective cohort study of patients presenting to the emergency department of the participating hospitals with suspected pandemic influenza during the second wave of the 2009 H1N1 pandemic. Patients were eligible for inclusion if they met the clinical diagnostic criteria of (1) fever (pyrexia ≥ 38°C) or a history of fever and (2) influenza-like illness (two or more of cough, sore throat, rhinorrhoea, limb or joint pain, headache, vomiting or diarrhoea) or severe and/or life-threatening illness suggestive of an infectious process.

Emergency department staff identified eligible patients and then completed a standardised assessment form that doubled as a clinical notes and study data collection form [referred to hereinafter as the clinical assessment form (CAF) and prepared in adult and paediatric variants – see Appendix 5]. It included the elements of the CURB-65 score, PMEWS, the swine flu hospital pathway and any other measures that could be routinely recorded in the emergency department (comorbidities, physiological observations, routine blood tests, ECG and chest radiograph). Details of any prepresentation antiviral medication, antibiotics and immunisation status were also recorded. The study did not involve any change to patient management, so patients were treated and then discharged home or admitted to hospital according to normal emergency department practices.

Patients were informed of the study by means of posters displayed in the emergency department, and leaflets distributed from reception and the pandemic influenza assessment area. They were informed that they could withdraw their data from the study but were not asked to consent to participate in the study. We did not seek patient consent to participate on the basis that the study was limited to collection of routinely available data and any delays in patient assessment could have risked compromising patient care.

Research staff followed patients up until 30 days after attendance by hospital record review and, if appropriate, general practitioner contact to identify patient outcomes. Data were abstracted from the CAF and hospital notes by researchers working with an honorary contract from the hospital Trust or researcher passport recognised by the Trust. The researcher kept a record of any patients who withdrew from the project. He/she entered anonymised data on to a secure online database provided by the Clinical Trials Unit at the University of Sheffield, Sheffield, UK. Other members of the research team had access only to anonymised data on the secure database.

The CAF constituted the clinical notes and was kept in each hospital according to normal practice. A copy of the CAF was retained by the researcher in a secure location in each hospital, to be destroyed 6 months after the end of the project. The Clinical Trials Unit will maintain an anonymised database until 10 years after the end of the project.

Outcome measures

Patients who died or required respiratory, cardiovascular or renal support during the 30-day follow-up were defined as having a poor outcome. Patients who survived to 30 days without requiring respiratory, cardiovascular or renal support were defined as having a good outcome. We also recorded whether they were treated with antiviral agents or antibiotics and the length and location of any hospital stay.

Respiratory support was defined as any intervention to protect the patient's airway or assist their ventilation, including non-invasive ventilation or acute administration of continuous positive airway pressure. It did not include supplemental oxygen alone or nebulised bronchodilators. Cardiovascular support was defined as any intervention to maintain organ perfusion (such as inotropic drugs) or invasively monitor cardiovascular status (such as central venous pressure, pulmonary artery pressure monitoring or arterial blood pressure monitoring). It did not include peripheral intravenous cannulation and/or fluid administration. Renal support was defined as any intervention to assist renal function, such as haemoperfusion, haemodialysis or peritoneal

dialysis. It did not include intravenous fluid administration.

Outcome assessment was based primarily on researcher review of hospital computer records and case notes. If there was no evidence of a poor outcome in these the patient was recorded as having a good outcome. If the outcome was uncertain (for example, if the patient was transferred to another hospital or left hospital against medical advice) the researcher contacted the patient's general practitioner for clarification.

Proposed sample size

The sample size depended upon the size and severity of the pandemic. We planned to collect data during the pandemic at four hospitals in Sheffield and Manchester covering a population of > 1 million. Prior to the pandemic, the Department of Health estimated that a 25% clinical attack rate with illustrative case hospitalisation and case fatality rates of 0.55% and 0.37%, respectively, suggested that a pandemic could lead to 12,500 emergency department attendances, 1400 hospitalisations and 900 excess deaths in our population.[1] If one-half of these occurred while we were collecting data then around 6000 cases with 600 poor outcomes would be available for analysis.

We planned to split the database for analysis into two data sets of equal size, one for developing new scores and testing existing scores, and one for comparing the new and existing scores. To develop a new triage method we estimated needing around 10 events per parameter tested in the model, so 200 cases with a poor outcome would allow us to test 20 parameters. A sample size of 283 cases with a poor outcome would ensure a power of 80% to compare an area under the ROC curve of 0.85 versus 0.90 at 5% significance, assuming a correlation of 0.6 between scores.[11]

Statistical analysis

Existing triage methods

We planned to assess CURB-65, PMEWS and the swine flu clinical pathway in adults and in children by calculating the AUROC (*C*-statistic) for discriminating between cases with and without a poor outcome (defined as death or need for support of respiratory, cardiovascular or renal function) and sensitivity and specificity at key decision-making thresholds. For each score we assumed a score of zero or a negative categorisation for any variable or criterion that was missing.

New triage methods

As outlined above, we planned to develop two new triage scores: one based on initial assessment only and the other based on all emergency department data. We planned to test the association of each potential clinical predictor variable with outcome and then undertake logistic regression to identify independent predictors of outcome. The strongest independent predictors of outcome would then be combined to form a new triage score. Continuous predictor variables would be divided into categories on the basis of the relationship of the variable with outcome. Integer weights would be assigned to each category of predictor variable according to the coefficient derived from a multivariate model using categorised independent predictors. This would generate a composite clinical score in which risk of poor outcome increases with the total score.

Chapter 3

Ethical and governance arrangements

The North West Research Ethics Committee (REC) and the National Information Governance Board (NIGB) reviewed and approved the study protocol. The University of Sheffield was the study sponsor. The Project Management Group (PMG), consisting of the coapplicants and the appointed research staff, managed the study. A steering group was appointed, consisting of the chief investigator, project manager, an independent clinician (Chairperson), statistician and layperson to provide independent oversight.

Study progress and changes to the protocol

The study commenced on 1 September 2009, after the first wave of the pandemic in July 2009 but before the second wave in October and November 2009. The Integrated Research Application System (IRAS) application form was completed and lodged in the system on 10 August 2009. On 11 August 2009 the REC debated the proposal and the project team received their written feedback on 18 August. Following the submission of the IRAS form, the South Yorkshire Comprehensive Local Research Network (CLRN) contacted the NIGB on 14 August 2009 to initiate discussions on 'fast tracking' the application, which they agreed to do. The chief investigator contacted the NIGB on the 17 August 2009 and the application form was delivered shortly after. First comments from the NIGB were issued on 24 August 2009. Responses by the chief investigator to the issues raised were returned to the NIGB on 4 September 2009 [together with the first draft of the System Level Security Policy (SLSP)]. Responses to issues raised by the REC were despatched on 7 September 2009. The NIGB referred the SLSP to their in-house security adviser, who, in turn, sent on further queries to the project team on 14 September 2009. A revised draft of the SLSP was prepared and sent back to the NIGB on 17 September 2009, which was accepted by the security adviser on 18 September 2009. Full NIGB approval was issued on the 22 September 2009 resulting in final approval from the REC being issued on 24 September 2009.

Running in tandem with the processing of ethics documentation was a parallel process of securing local governance approval from the four participating sites. The 'R&D' part of the IRAS form was received by the national CLRN responsible for England on 4 September 2009. Arrival of this form triggered notifications to the Greater Manchester CLRN and the South Yorkshire CLRN, who, in turn, liaised with the Trusts within their jurisdiction concerning the local approvals. The lead investigators at each site concurrently submitted Site Specific Information (SSI) forms, (generated through IRAS) to their own research departments.

The dates of initiation for the local approvals process were:

- 4 September 2009 CLRN received the IRAS R&D form
- 15 September 2009 Sheffield Teaching Hospitals SSI form submitted
- 25 September 2009 Sheffield Children's Hospital SSI form submitted
- 15 October 2009 Pennine Acute Hospitals SSI form submitted
- 25 November 2009 University Hospitals of South Manchester SSI form submitted.

Research governance approval was secured at each site on the following dates:

- 10 November 2009 Sheffield Teaching Hospitals
- 11 November 2009 Pennine Acute Hospitals
- 26 November 2009 University Hospitals of South Manchester
- 22 December 2009 Sheffield Children's Hospital.

There were delays in securing the individual Trust approvals. These delays resulted from the requirements of each Trust's research governance procedures (involving forms for project registration, finance and data protection each requiring 'wet ink' signatures) and the problems of a process developed for interventional studies, such as clinical trials (with associated Good Clinical

Practice training, Standard Operating Procedures, delegation logs and enhanced Criminal Records Bureau checks for research field staff) being inappropriately applied to data-based research.

In the period between main REC and NIGB approval being granted and the local approvals coming through, the chief investigator and the local investigators at three sites took the decision to use the REC-approved CAF for routine clinical assessment of cases of suspected pandemic influenza. The forms were distributed around the participating emergency departments, together with the patient information leaflets and information posters, and staff were advised to use the forms for clinical assessment, as outlined in the study protocol. Examining doctors followed the procedures agreed with the REC and the NIGB on informing patients about the study and pointing out the individual's right to withdraw should they wish to do so. We felt that it was appropriate to take this initiative because had we waited for granting of research governance approval we might have missed the second wave of the pandemic and the opportunity to collect valuable data. We were unable to start data collection at the fourth hospital until after the second wave had passed, so this hospital did not contribute to the study.

In summary, the process of REC review was efficient, reflecting the activation of an emergency policy by the National Research Ethics Service. NIGB review was also efficient, although the requirements of submission (such as the need for a SLSP) would have prevented researchers with no previous experience of using confidential data without consent from undertaking rapid submission. The process of securing local UK NHS approvals was slow and inefficient. This contrasts with experience reported by other pandemic studies,[12] where, for example, one multicentre study apparently obtained local approvals within 5 days in over 100 hospitals.

The pandemic was much less severe than predicted. As of 5 January 2010 there had been 28,456 laboratory-confirmed cases of H1N1 influenza, with 4930 reported as being hospitalised and 355 deaths.[13] However, serological testing in children has shown that clinical surveillance may identify only one in 10 cases of H1N1 infection, and around one child in every three was infected with 2009 pandemic H1N1 in the first wave of infection in regions with a high incidence.[14] The low numbers of hospitalisations and deaths therefore reflect lack of disease severity rather than lack of disease in the community. This meant that instead of the predicted 1400 hospitalisations and 900 excess deaths in our population it was likely that the pandemic would only have resulted in around 80–90 hospitalisations and 5–6 deaths if our population were typical of the UK (estimated by multiplying total UK hospitalisations and deaths by the approximate proportion of the UK population covered by the participating hospitals).

It became apparent during the study that the sample size would be markedly less than our original prediction and the study would be underpowered. In an attempt to address this we proposed a change to the study methods and amended the protocol accordingly. We proposed using routine hospital data collection systems to retrospectively identify all patients who presented to all four hospitals with symptoms consistent with suspected pandemic influenza during both waves of the pandemic and suffered a poor outcome (as defined above). This would allow us to use a case–control approach, with a maximised number of cases and thus optimise the statistical power of the study within the available resources and caseload. However, this approach would involve a substantial change to methodology and the need to use data without informing patients. We therefore submitted the amended protocol for review by the REC and the NIGB. The notice of substantial amendment is shown in Appendix 6.

In response, the NIGB requested that a new application for section 251 support be submitted to their next Ethics and Confidentiality Committee (ECC) meeting and stated that the ECC position on retrospective studies of relatively small numbers of patients was that consent should be sought via the members of the direct clinical care team involved in the care and treatment of the individual cohort. There was also an expectation that consent should be sought from the family of patients who were deceased. If consent were not feasible (and this would only be accepted if strong justification were provided), data extraction from the clinical record would need to be carried out by the direct clinical care team and only fully anonymised data returned to the researchers. The REC rejected the proposed amendment pending the decision of the NIGB, and also suggested that informed consent to the use of data should be requested from those who had not died. Responses from the NIGB and REC are in Appendices 7 and 8, respectively.

We decided that, based on these responses, we would not be able to undertake a meaningful

study with section 251 support using the proposed case–control methodology. We had some ethical concerns about contacting recently bereaved family members, as suggested by the NIGB, but accepted that there were no insurmountable barriers to seeking consent, so we could not claim this was not feasible. However, we anticipated that a substantial proportion of patients or relatives would not respond to our request for consent and subsequent responder bias would render the findings of the study worthless, or at least of such limited value as to not justify the expense of the project or intrusion into patients' and relatives' lives. Furthermore, clinical staff in the participating hospitals indicated that they were neither willing nor able to commit time to extract data from the clinical records. We therefore proceeded with the initial investigation plan. Our reply is in Appendix 9.

Chapter 4
Results

As insufficient cases presented to the participating hospitals to complete our initial analysis plan, we have restricted our analysis to the ability of the various existing triage tools to predict hospital admission and poor outcome.

Cases were identified and data collected at the Northern General Hospital between 29 September 2009 and 10 January 2010, Sheffield Children's Hospital between 10 October 2009 and 31 December 2009 and South Manchester between 24 September 2009 and 7 February 2010. We identified and collected data from a total of 492 cases, 11 of whom asked for their data to be withdrawn, leaving 481 for analysis. There were 77 cases at the Northern General Hospital, 226 at the Sheffield Children's Hospital and 178 at South Manchester. Ages ranged from infant to 96 years. Most of the cases were children, with 347 out of 481 (72%) aged 16 years or less. The modal age group was 1–2 years, accounting for 69 out of 481 (14%). There were 237 females (49%) and 244 males (51%). Most patients self-referred (399/481, 83%), while only 41 (8%) were referred via their GP and 15 (3%) were referred via NHS Direct.

Symptom duration was recorded for 379 patients. Mean duration was 3.1 days, median was 2 days and most patients (213 out of 379, 56%) had 1–2 days of symptoms. Prior to their index hospital attendance, 30 (6%) had attended hospital with the same complaint, eight patients (2%) had received vaccination against H1N1, 39 (8%) had been given oseltamivir, and 46 (10%) had been given antibiotics, although not always specifically for their presenting complaint.

Social isolation (defined as living alone or having no fixed abode) was reported by 12 (2%). *Table 1* shows the proportion reporting different levels of performance status. This was not recorded for one-third of patients but most cases that did report it had unrestricted normal activity. *Table 2* shows the proportion reporting chronic disease or medication use. The only chronic problem recorded with any frequency was asthma, in 13% of cases.

Influenza was thought by the physician to be the most likely diagnosis in 214 out of 368 cases (58%). The most common alternatives were upper respiratory tract infection (79 cases) and tonsillitis (23 cases).

TABLE 1 *Proportion reporting different levels of performance status (self or parental report)*

Performance level	*n* (%)
Unrestricted, normal activity	223 (46)
Limited strenuous activity, can do light	46 (10)
Limited activity, can self-care	34 (7)
Limited self-care	11 (2)
No self-care	4 (1)
Not recorded	163 (34)
Total	481 (100)

TABLE 2 *Proportion reporting chronic disease or medication use (n = 481)*

Chronic problem	*n* (%)
Heart disease	4 (1)
Lung disease	6 (1)
Renal impairment	1 (< 1)
Steroid therapy	9 (2)
Asthma	61 (13)
Diabetes	7 (1)
Malignancy	4 (1)
Immunosuppression	4 (1)

Presenting physiological features were not recorded in all cases. Temperature ($n = 425$) ranged from 35.0°C to 40.7°C [mean 37.8, standard deviation (SD) 1.1] and peripheral oxygen saturation ($n = 369$) ranged from 79% to 100% (mean 97%, SD 6%). Some 19 out of 369 (5%) cases had peripheral oxygen saturation below 94%. Results for pulse rate, respiratory rate and blood pressure (*Table 3*) are categorised by age group to allow for age-related variation in normal values for these parameters. Tachycardia and tachypnoea were relatively common, whereas blood pressure was generally normal.

Variables that were relevant only to younger children were present as follows: 6 out of 207 (3%) had been managed on a special care baby unit, 8 out of 234 (3%) had not had their routine vaccinations, 51 out of 227 (22%) were not taking feeds and 47 out of 205 (23%) of clinicians reported parental anxiety as being a concern.

Blood tests were only ordered for 55 out of 481 cases (11%). The results are summarised in *Table 4*. Chest radiographs were ordered and were abnormal in 12 cases, normal in 19, not done in 284 and not recorded in 166. An ECG was ordered and abnormal in 10 cases, normal in 24, not done in 67 and not recorded in 380.

The clinical plan included oseltamivir for 58 cases and antibiotics for 56 (22 amoxicillin, nine augmentin, one cefotaxime, two ceftriaxone, three clarithromycin, one gentamycin and 18 penicillin). The attendance resulted in admission for 83 out of 481 cases (17%): 12 aged 0–1 years, 14 aged 2–5 years, 13 aged 6–16 years and 44 adults.

Tables 5 and *6* show the CURB-65 scores and PMEWS scores (adults only). The recommended threshold for admission[4] for CURB-65 is a score of two or more. *Table 5* suggests that 9 out of 134 (7%) of patients should have been admitted. Applying a similar threshold for PMEWS would have resulted in 81 out of 134 (60%) being admitted.

Patients with a higher CURB-65 score were more likely to be admitted ($p = 0.001$, chi-squared test for trend): 25 out of 101 (25%) with a score of zero, 11 out of 24 (46%) with a score of one, 7 out of 8 (88%) with a score of two and the patient with a score of three were admitted. Admitted patients had a higher mean PMEWS scores (4.6 vs 2.0, $p < 0.001$, *t*-test). The *C*-statistics for CURB-65, PMEWS and the swine flu hospital pathway in adults in terms of discriminating between those admitted and discharged were 0.65 (95% CI 0.54 to 0.76), 0.76 (95% CI 0.66 to 0.86) and 0.62 (95% CI 0.51 to 0.72), respectively.

TABLE 3 *Presenting physiological features*

		Age			
		0–1 years (*n* = 87)	**2–5 years (*n* = 135)**	**6–16 years (*n* = 125)**	**> 16 (*n* = 134)**
Pulse rate (*n* = 424)	Mean (SD)	147 (24)	130 (24)	113 (22)	100 (18)
	Range	108–204	80–196	72–182	62–152
Respiratory rate (*n* = 390)	Mean (SD)	35 (10)	28 (8)	23 (6)	20 (6)
	Range	20–62	16–60	12–52	12–40
Systolic BP (*n* = 141)	Mean (SD)	–	–	118 (14)	128 (19)
	Range	–	–	92–140	80–188
Diastolic BP (*n* = 140)	Mean (SD)	–	–	63 (12)	73 (12)
	Range	–	–	40–78	38–111

BP, blood pressure. This was recorded in only one child aged 0–1 years and four children aged 2–5 years.

TABLE 4 *Summary of blood results*

Blood test	Mean (SD)	Range	Extreme values
Haemoglobin (g/dl)	13.6 (2.1)	6.5–17.0	4 < 11.0
White cell count ($\times 10^9$/l)	10.3 (7.2)	1–50	4 < 4.0, 21 > 10.0
Platelet count ($\times 10^9$/l)	228 (84)	38–452	7 < 150, 2 > 400
Sodium (mmol/l)	136 (4)	119–142	12 < 135
Potassium (mmol/l)	4.1 (0.5)	3.2–5.7	7 < 3.5, 1 > 5.5
Urea (mmol/l)	11.4 (41.2)	1.4–305.0	11 > 6.5
Creatinine (μmol/l)	89 (71)	44–569	6 > 120

TABLE 5 *CURB-65 scores for adults*

CURB-65 score	*n* (%)
0	101 (75)
1	24 (18)
2	8 (6)
3	1 (1)
Total	134 (100)

TABLE 6 *PMEWS scores for adults*

PMEWS score	*n* (%)
0	24 (18)
1	29 (22)
2	21 (16)
3	15 (11)
4	9 (7)
5	15 (11)
6	6 (4)
7	3 (2)
8	9 (7)
9	2 (1)
10	1 (1)
Total	134 (100)

Tables 7 and *8* show the results for adults and children (aged 16 or less), respectively, on the swine flu hospital pathway, along with the number and proportion with each criterion admitted. Among the adults, 16 out of 28 (57%) with a positive criterion were admitted, compared with 28 out of 106 (26%) with no positive criteria. Among the children, 14 out of 39 (36%) with a positive criterion were admitted, compared with 25 out of 308 (8%) with no positive criteria.

Only 5 out of 481 (1%) patients had a poor outcome according to our definition. Their details are as follows:

1. Female, aged 60, no chronic illnesses, presented with respiratory rate 30, heart rate 90, temperature 38.0, blood pressure 160/62, peripheral oxygen saturation 90%, Glasgow Coma Score (GCS) 15, haemoglobin 13.4, platelets 198.0, white cell count 12.7, sodium 119.0, potassium 4.4, urea 12.9, creatinine 102.0, chest radiograph abnormal, CURB-65 score 2, PMEWS score 6, positive for swine flu hospital pathway criterion C, died 5 days after admission.

TABLE 7 *Swine flu hospital pathway criteria for adults*

Criterion	*n* (%) meeting criterion	*n* admitted (% admitted of those meeting criterion)
A	2 (1)	2 (100)
B	7 (5)	5 (71)
C	11 (8)	9 (82)
D	2 (1)	1 (50)
E	12 (9)	4 (33)
F	3 (2)	3 (100)
G	3 (2)	2 (66)
Any category positive	28 (21)	16 (57)

TABLE 8 *Swine flu hospital pathway criteria for children*

Criterion	*n* (%) meeting criterion	*n* admitted (% of those meeting criterion)
A	0	–
B	23 (7)	9 (39)
C	4 (1)	2 (50)
D	0	–
E	10 (3)	2 (20)
F	0	–
G	6 (2)	3 (50)
Any category positive	39 (11)	14 (36)

2. Female, aged 43, known asthma, presented with respiratory rate 22, heart rate 95, temperature 39.2, blood pressure 188/111, peripheral oxygen saturation 95%, GCS 15, haemoglobin 15.3, platelets 275.0, white cell count 14.0, sodium 138.0, potassium 4.2, urea 3.4, creatinine 100.0, chest radiography performed but findings not recorded, CURB-65 score 0, PMEWS score 5, negative for all swine flu hospital pathway criteria, required non-invasive ventilation.
3. Male, aged 39, known renal failure, presented with respiratory rate 16, temperature 38.7, haemoglobin 11.7. platelets 38, white cell count 1.0, sodium 132.0, potassium 4.3, urea 14.8, creatinine 569.0, chest radiography performed but findings not recorded, CURB-65 score 1, PMEWS score 1, negative for all swine flu hospital pathway criteria, required non-invasive ventilation. Also required haemodialysis for pre-existing renal failure.

TABLE 9 *Sensitivity and specificity of existing triage methods*

		Sensitivity (95% CI)	Specificity (95% CI)
CURB-65	Score > 1	20% (4 to 62)	94% (88 to 97)
PMEWS	Score > 1	80% (38 to 96)	40% (32 to 49)
Swine flu hospital pathway	Any criterion positive	60% (23 to 88)	81% (73 to 87)

4. Female, aged 25, known epilepsy, presented with respiratory rate 22, heart rate 90, blood pressure 80/40, temperature 37.5, peripheral oxygen saturation 79%, GCS 15, haemoglobin 11.8. platelets 75, white cell count 1.7, sodium 136.0, potassium 3.2, urea 4.7, creatinine 53.0, chest radiography not recorded, ECG not recorded, CURB-65 score 1, PMEWS score 7, positive for swine flu hospital pathway criteria C and E, required positive pressure ventilation and then died after 54 days.
5. Female, aged 51, known chronic lung disease, presented with respiratory rate 36, heart rate 135, temperature 37.8, blood pressure 116/80, peripheral oxygen saturation 95%, GCS 15, haemoglobin 15.3. platelets 247, white cell count 10.0, sodium 136.0, potassium 3.8, urea 4.4, creatinine 85.0, chest radiography not recorded, ECG abnormal, CURB-65 score 1, PMEWS score 8, positive for swine flu hospital pathway criterion B, required non-invasive ventilation and positive pressure ventilation.

All five patients were admitted to hospital at the initial attendance. CURB-65 scores were zero, one (three cases) and two. PMEWS scores were one, five, six, seven and eight. The swine flu hospital pathway was positive for three cases and negative for two. The *C*-statistic for each method was CURB-65 0.78 (95% CI 0.58 to 0.99), PMEWS 0.77 (95% CI 0.55 to 0.99) and the swine flu hospital pathway 0.70 (95% CI 0.45 to 0.96). *Table 9* shows sensitivity and specificity for CURB-65 and PMEWS, with a threshold of > 1 and the swine flu hospital pathway with any criterion positive.

A further four adults and one child were admitted to critical care environments, but did not have interventions qualifying for our definition of a poor outcome. One other adult was admitted to the intensive therapy unit, but no specific interventions were recorded.

There were insufficient data for multivariate analysis to determine which clinical features and tests were independent predictors of outcome or develop new triage methods.

Chapter 5
Discussion

The number of cases of suspected pandemic influenza was much lower than predicted and the number of cases with a poor outcome was lower still. We identified two deaths and three patients who survived after requiring respiratory support among those who presented to the emergency departments of three hospitals during the second wave of the pandemic. All five cases were adults. The CURB-65 score and swine flu hospital pathway did not reliably detect these cases. A CURB-65 score of two or more has been recommended to trigger admission.[4] In our study the CURB-65 score was two or more in 7% of the adult patients and one of the five cases with a poor outcome. The swine flu hospital pathway was positive for 21% of the adult patients and three out of five cases with a poor outcome. The PMEWS score does not have a recommended threshold but a threshold of two or more has been suggested (K Challen, University Hospitals of South Manchester, May 2010, personal communication). According to this threshold PMEWS would be positive in 60% of the adult patients and four out of five cases with a poor outcome.

The findings are substantially limited by the small sample and, in particular, only including five cases with a poor outcome. These five cases may have been atypical, so we can draw no firm conclusions regarding the value of these three triage tools, other than raise some concerns about the discriminant value of existing triage methods. Furthermore, we did not test the application of the methods in practice, but calculated or inferred their performance from clinical data. Some criteria, such as the swine flu hospital pathway criterion G (other clinical concern), may have identified some of the cases with a poor outcome when used in practice.

We did not require virological testing or confirmation as both national and local guidance recommended that patients with influenza-like illness fulfilling the HPA criteria (which we used as our inclusion criteria) should be assumed to be suffering from H1N1 influenza and treated accordingly. Our aim was to complete pragmatic 'real world' research, reflecting as closely as possible standard working conditions. We did not use hospital admission as an outcome because we thought that this would be heavily influenced by the triage method in use. However, it is interesting to note that CURB-65 and the swine flu hospital pathway appeared to discriminate poorly between those admitted and those discharged, despite being recommended for use in triage to hospital admission. It appears that clinicians in the participating hospitals were basing their decisions on other criteria.

The study was unable to deliver on its main objectives because the caseload arising from the pandemic was much smaller than predicted. The Department of Health prepandemic planning assumptions used a base scenario of a cumulative attack rate of 25% of the population over one or more waves of 15 weeks each, with a 0.37% case fatality rate.[1] This was based on the occurrence in previous UK pandemics of an attack rate of 25–35%, and case fatality of 0.2–2%.[1] Based on data from Mexico in early 2009, the critical care bed requirement was calculated to be 140% of capacity in North West England and 160% of capacity in Yorkshire.[15] The first clinical data from Mexico in March–April 2009 demonstrated a 10- to 11-fold increase in severe pneumonia mortality in the 20- to 30-year-old age group.[16] Similarly, intensive care admissions in Australia and New Zealand were 28.7 cases per million population (15 times the normal admission rate for viral pneumonitis) in winter (June–August) 2009.[17] First-wave hospitalisations in Ontario, Canada, resulted in a 25% intensive care admission rate,[18] as did the first 272 hospitalisations in the USA, with the USA also reporting a 7% mortality rate.[19] However, the second pandemic wave in Mexico in June–July 2009 demonstrated much lower severity and mortality rates, possibly due to earlier antiviral treatment coincident with a nationwide publicity campaign.[20] Similarly, there were no fatalities in the first 426 hospitalised cases in China, and only a 3.9% attack rate in screened close contacts.[21] Worldwide case severity, hospitalisation and mortality rates were all low, and in fact lower than seasonal influenza in some countries.[22]

It is unclear why the experience in the UK was not similar to that in Australasia. Retrospective

immunological examination of samples taken pre-pandemic (2008 and early 2009) showed protective levels of antibody to the pandemic H1N1 influenza strain in 23% of patients aged over 65 years.[23] This presumably represents crossreactivity from previous H1N1 exposure. However, there were significant pockets of H1N1 activity, notably in Birmingham and London. As of 18 March 2010, 342 deaths due to H1N1 influenza had been reported in England. Birmingham Heartlands Hospital reported that 7 out of 78 inpatients had required intensive care admission (including two patients requiring extracorporeal membrane oxygenation),[24] and serological testing demonstrated an odds ratio of 5.23 for exposure to the H1N1 virus in the West Midlands (using East Midlands as a referent group).[23]

There are a number of potential explanations for the lack of similar findings in the North West and Yorkshire. It may be that our inclusion criteria (derived from the HPA case definition) excluded a significant number of patients who were, in fact, infected with the H1N1 virus. It is notable that 29 out of 71 children admitted to hospital in Birmingham did not fulfil the HPA criteria.[25] As Birmingham and London were early hotspots it may be that the populations of Manchester and Sheffield were more aware of the availability of antiviral agents and therefore sought treatment earlier and mitigated the severity of their infection. There may also be confounding factors in terms of local viral evolution and pre-existing local population health that will be explored by other national projects, such as Flu-CIN (Influenza Clinical Information Network).

Although the lack of available cases was the main reason for the failure to address the main research questions, the study was also hampered by delays in acquiring research governance approval and our inability to find a case–control method that was both acceptable to the NIGB and REC and likely to yield worthwhile results. Our experience contrasts with other studies undertaken during the pandemic. At the start of the H1N1 swine influenza pandemic, participating case mix programme units were asked to submit data for confirmed H1N1 cases for rapid analysis and feedback. In addition, the Intensive Care National Audit and Research Network (ICNARC) gained ethics and research regulatory approval within 6 weeks for approximately 250 acute hospitals to collect data on critical care admissions with confirmed or suspected H1N1 influenza.[26] This process was presumably facilitated by existing ICNARC data management processes that support routine critical care audit and allow collection of anonymised data. This highlights the importance of having routine collection of audit and research data and the need to develop similar systems in emergency care. It also highlights the need to have research centres with established expertise in data processing and management. We would not have been able to meet the requirements of the NIGB within a practical timeframe were it not for our previous experience of applying for approval for a similar project.

This study also highlights the value of having reliable estimates of pandemic size and severity to assist sample size estimates. Predictions of pandemic size and severity are inevitably subject to substantial uncertainty. We could be justifiably criticised for not taking this uncertainty into account in planning this project. Future proposals for pandemic research should base sample size estimates on the full range of potential scenarios, including the possibility of no significant pandemic. Simulation methods could be useful to explore the potential value of different research methods in a range of different scenarios. These could be used to refine the research question and focus data collection upon the most useful variables, and guide adaptation of the study design as the pandemic emerges. However, it is important that simulation and analysis of different scenarios takes place well in advance of any emerging pandemic. Our proposal was developed over a few weeks in response to the emerging 2009 H1N1 pandemic, leaving no time for sophisticated protocol development. Future pandemic research should be planned and any preparatory work undertaken before the next pandemic emerges. In a similar vein, pilot data would have been helpful for protocol development and sample size estimates. However, the unpredictable nature of a pandemic means that the only opportunity to collect pilot data may also represent the only opportunity to undertake the full project. Some piloting could be undertaken prior to a pandemic, such as developing systems for data collection and protection and addressing information governance requirements. Undertaking this pilot work prior to the emergence of a pandemic could allow research to commence in a quick and efficient manner when a pandemic occurs.

As the 2009–10 H1N1 pandemic in the UK has not produced adequate numbers of severely ill patients from which to draw robust conclusions, health service planners must revert to the pre-existing evidence base. This includes information from

multiple sources: non-flu risk stratification tools, SARS and H5N1, and international experience of H1N1.

Pre-pandemic advice advocated the use of pneumonia severity scores to risk stratify influenza patients.[3] Some evidence exists to support their use in identifying patients who are likely to require critical care facilities; the Pneumonia Severity Index predicts critical care admission with AUROC scores of 0.6[27]–0.75[28] and CURB-65 similarly achieves AUROC scores of 0.61[29]–0.77.[30] Other tools designed specifically to predict requirement for critical care exist,[31–32] but have yet to be fully validated. However, in extrapolating from pneumonia-specific severity scores, it should be remembered that atypical presentation was well recognised in H5N1 patients.[33] A significant minority of both paediatric and adult patients eventually diagnosed with H1N1 did not fulfil HPA screening criteria, notably for pyrexia.[25,34] Little literature exists on risk assessment of undifferentiated emergency patients, and what there is concentrates on mortality risk.[35–37]

It appears from the international experience that obesity,[17] pre-existing comorbidity[19] and pregnancy[17,38] convey a worse prognosis during pandemic influenza infection. A single study of bacterial pneumonic superinfection in influenza from Taiwan identified shock, respiratory rate of over 24 breaths/minute, acidosis, raised creatinine and a pneumonia severity index of class IV or V as indicators of poor prognosis.[39]

The SARS outbreaks in South-East Asia and Toronto, Canada, highlighted the importance of developing surge capacity in the hospital and critical care spheres, and of being able to alter institutional priorities.[40] Changes in working pattern were particularly driven by high risks of nosocomial viral transmission.[41] The surge capacity and resilience of the NHS was not severely tested by the 2009–10 A/H1N1 influenza virus outbreak, except in isolated pockets. However, there were significant problems identified with misdiagnosis and missed diagnoses during the outbreak.[42]

Emergency departments should remain prepared to deal with patients with diffuse non-specific symptomatology from influenza, and retain the capability to cohort these potentially infectious patients in the emergency department and the hospital. Risk assessment will still take place in an absence of evidence but should be guided by information from the international experience.

Chapter 6
Conclusions

We can draw no reliable conclusions from the data available, other than raise potential concerns about existing triage methods for patients with suspected pandemic influenza. Our very limited data suggest that these methods may fail to discriminate between patients who will have an adverse outcome and those with a benign course. Furthermore, clinicians in our study did not generally appear to admit or discharge on the basis of these tools, despite being recommended for use in the pandemic.

Implications for practice

Currently available triage methods for patients with suspected pandemic influenza are not supported by sufficient data to allow them to be recommended for routine use. In the absence of evidence for the use of these triage tools, emergency department clinicians should continue to base triage decisions for patients with suspected pandemic influenza upon their clinical judgement.

Recommendations for research

Further research is clearly required to evaluate existing triage tools and develop new methods. This should remain a priority in future waves of the 2009 H1N1 pandemic and any future pandemics. However, the barriers to progress encountered by this study raise concerns about the ability of the NHS to undertake this research. Delays in acquiring research governance approval slowed progress generally and prevented data collection at one hospital. If the pandemic had developed as anticipated, these delays could have been critical to the success of the project. Despite the experience gained in this project we are not confident that it could be successfully undertaken in a full-scale pandemic. Alternative ways of evaluating triage methods should therefore be explored. These could include evaluation in surrogate conditions, such as seasonal flu or pneumonia, and the development of simulation techniques to explore the application of triage methods to theoretical scenarios.

The need to limit access to patient data is important to ensure that public trust in research is maintained. However, the requirements of information governance may limit our ability to undertake potentially valuable research. The public need to be informed of the potential trade-off between data protection and NHS research, and involved in determining when patient data can be used for research purposes without consent. Research could be helpful in exploring public attitudes to the use of patient data for research purposes, developing information systems that allow researchers to access anonymised data, and piloting data collection and protection processes.

It is essential that this research is planned, and, where possible, undertaken prior to the emergence of the next pandemic. Our study has highlighted the difficulties of planning and undertaking research in an emerging pandemic. If future pandemic research is not planned or undertaken until the next pandemic emerges we can expect that similar difficulties will be encountered.

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Contributions of authors

SG and KC conceived the study; SG, KC, MC and the management group designed the study; RW managed the project; RW and KC oversaw data collection; SG and MC analysed the data; SG drafted the report, and all authors contributed to writing the report and approved the final draft.

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Appendix 1

CURB-65 score

One point each for:

- **C**onfusion
- **U**rea > 7 mmol/l
- **R**espiratory rate ≥ 30/minute
- **B**lood pressure: low systolic (< 90 mmHg) or diastolic (≤ 60 mmHg)
- age ≥ **65** years.

Appendix 2

Pandemic Modified Early Warning Score (PMEWS)

PLUS

Physiological Data (MEWS)
Ring 1 value for each factor

SCORE	3	2	1	0	1	2	3
Resp Rate	≤ 8			9-18	19-25	26-29	≥ 30
O2 Sats	<89	90-93	94-96	>96			
Heart Rate	≤ 40	41-50		51-100	101-110	111-129	≥ 130
Systolic BP	≤ 70	71 - 90	91 - 100	>100			
Temp		≤35.0	35.1-36	36.1-37.9	38-38.9	≥ 39	
Neuro				Alert	Confused Agitated	Voice	Pain Uncon

Total P-MeWS =

Patient Data

Score 1 for each factor

Age >65 ... ... ☐

Social Isolation ... OR ... ...
Lives alone/No fixed abode

Chronic Disease ... OR ... .. ☐
Respiratory, cardiac, renal, immunosuppressed, DM

Performance Status >2 ...

Normal activity without restriction	1
Strenuous activity limited, can do light	2
Limited activity but capable of self care	3
Limited activity, limited self care	4
Confined to bed/chair, no self care	5

Appendix 3

Community Assessment Tool for Adults

Criteria label	ADULTS WILL BE CONSIDERED FOR ADMISSION AT THE NEAREST GENERAL HOSPITAL IF THEY PRESENT WITH ANY OF THE FOLLOWING:
A	**Severe respiratory distress** Severe breathlessness, e.g. unable to complete sentences in one breath. Use of accessory muscles, supra-clavicular recession, tracheal tug or feeling of suffocation.
B	**Increased respiratory rate** measured over at least 30 seconds. Over 30 breaths per minute.
C	**Oxygen saturation ≤92% on pulse oximetry, breathing air *or* on oxygen** Absence of cyanosis is a poor discriminator for severe illness.
D	**Respiratory exhaustion** New abnormal breathing pattern, e.g. alternating fast and slow rate or long pauses between breaths.
E	**Evidence of severe clinical dehydration or clinical shock** Systolic blood pressure <90mmHg and/or diastolic blood pressure <60mmHg. Sternal capillary refill time >2 seconds, reduced skin turgor.
F	**Altered conscious level** New confusion, striking agitation or seizures.
G	**Causing other clinical concern to the clinical team or specialist doctor** e.g. a rapidly progressive or an unusually prolonged illness.

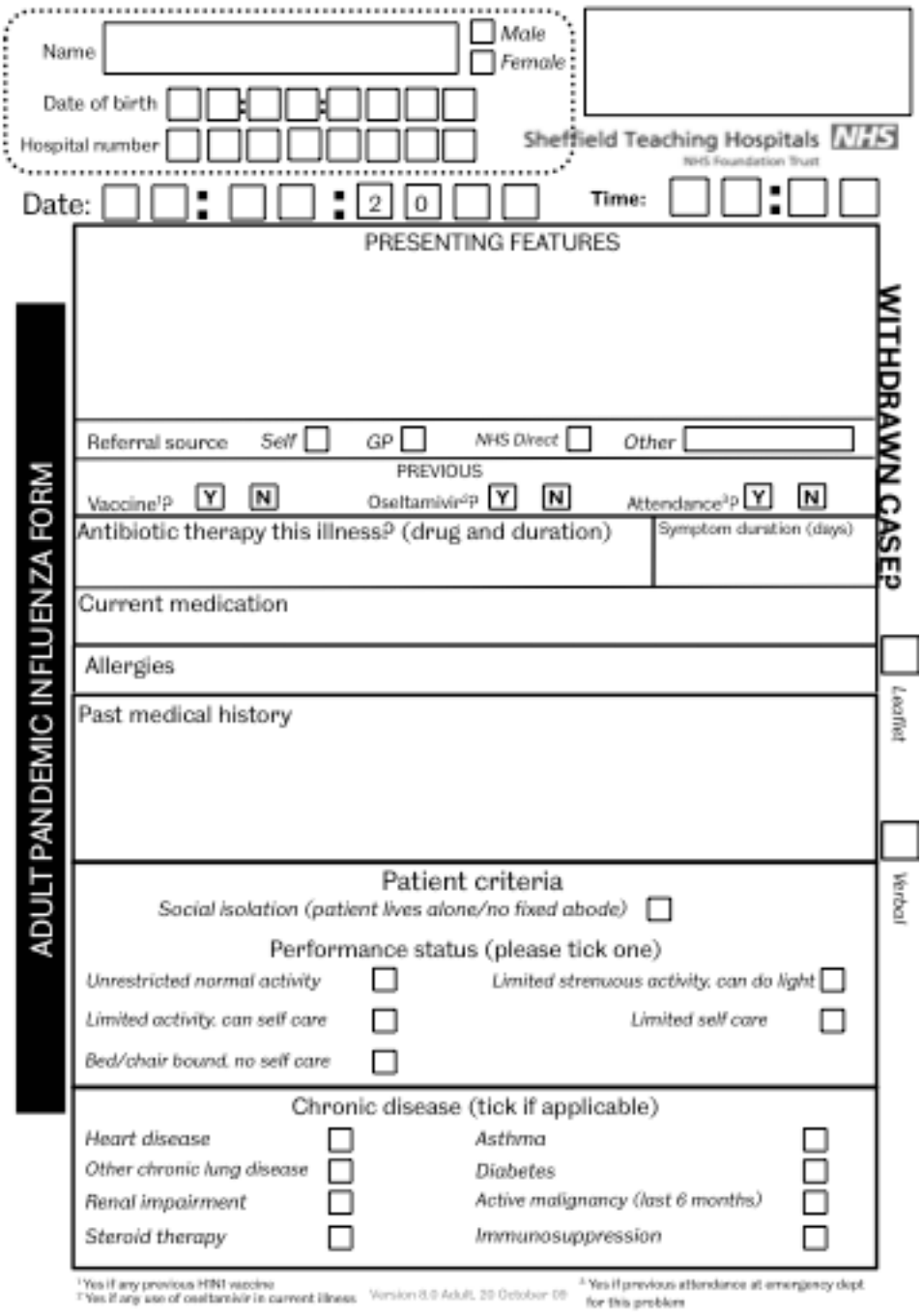
Appendix 4

Community Assessment Tool for Children

Criteria label	CHILDREN UNDER 16 YEARS OLD WILL BE CONSIDERED FOR ADMISSION AT THE NEAREST GENERAL HOSPITAL IF THEY PRESENT WITH ANY OF THE FOLLOWING:
A	**Severe respiratory distress** Lower chest wall indrawing, sternal recession, grunting, or noisy breathing when calm.
B	**Increased respiratory rate** measured over at least 30 seconds. ≥50 breaths per minute if under 1 year, or ≥40 breaths per minute if ≥1 year.
C	**Oxygen saturation ≤92% on pulse oximetry, breathing air or on oxygen** Absence of cyanosis is a poor discriminator for severe illness.
D	**Respiratory exhaustion or apnoeic episode** Apnoea defined as a ≥20 second pause in breathing.
E	**Evidence of severe clinical dehydration or clinical shock** Sternal capillary refill time >2 seconds, reduced skin turgor, sunken eyes or fontanelle.
F	**Altered conscious level** Strikingly agitated or irritable, seizures, or floppy infant.
G	**Causing other clinical concern to the clinical team or specialist doctor** e.g. a rapidly progressive or an unusually prolonged illness.

Appendix 5

Clinical Assessment Form (CAF)



Name ☐ Male ☐ Female

Date of birth ☐☐:☐☐:☐☐☐☐

Hospital number ☐☐☐☐☐☐☐☐

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

Date: ☐☐:☐☐:20☐☐ Time: ☐☐:☐☐

ADULT PANDEMIC INFLUENZA FORM

PRESENTING FEATURES

WITHDRAWN CASE? ☐ Leaflet ☐ Verbal

Referral source Self ☐ GP ☐ NHS Direct ☐ Other ☐

PREVIOUS

Vaccine[1]? Y ☐ N ☐ Oseltamivir[2]? Y ☐ N ☐ Attendance[3]? Y ☐ N ☐

Antibiotic therapy this illness? (drug and duration) | Symptom duration (days)

Current medication

Allergies

Past medical history

Patient criteria

Social isolation (patient lives alone/no fixed abode) ☐

Performance status (please tick one)

Unrestricted normal activity ☐ *Limited strenuous activity, can do light* ☐

Limited activity, can self care ☐ *Limited self care* ☐

Bed/chair bound, no self care ☐

Chronic disease (tick if applicable)

Heart disease ☐ *Asthma* ☐

Other chronic lung disease ☐ *Diabetes* ☐

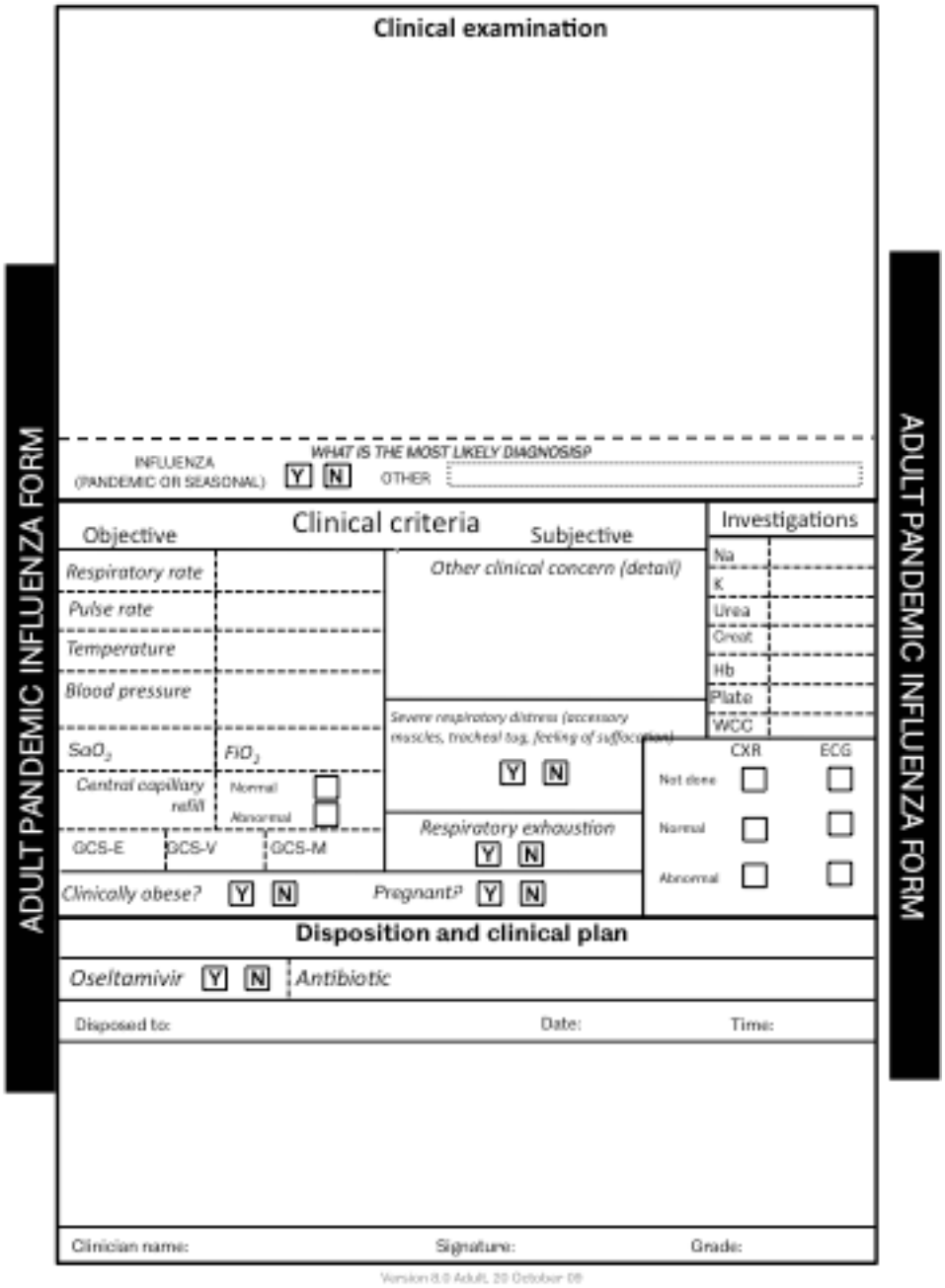
Renal impairment ☐ *Active malignancy (last 6 months)* ☐

Steroid therapy ☐ *Immunosuppression* ☐

[1] Yes if any previous H1N1 vaccine
[2] Yes if any use of oseltamivir in current illness

Version 8.0 Adult, 20 October 09

[3] Yes if previous attendance at emergency dept for this problem



Appendix 6

Notice of substantial amendment submitted to NIGB and REC

Details of Chief Investigator:	
Name:	Prof. Steve Goodacre
Address:	Health Services Research, ScHARR, University of Sheffield, Regent Court, Sheffield S1 4DA, UK
Telephone:	0114 2220842
Email:	s.goodacre@sheffield.ac.uk
Fax:	
Full title of study:	Pandemic Influenza Triage in the Emergency Department
Name of main REC:	North West 5 Main Research Ethics Committee
REC reference number:	09/H1010/60
Date study commenced:	19 October 2009
Protocol reference *(if applicable)*, current version and date:	version 0.003, 20 August 2009
Amendment number and date:	2; 29 January 2010

Summary of changes

Briefly summarise the main changes proposed in this amendment using language comprehensible to a layperson. Explain the purpose of the changes and their significance for the study. In the case of a modified amendment, highlight the modifications that have been made.

If the amendment significantly alters the research design or methodology, or could otherwise affect the scientific value of the study, supporting scientific information should be given (or enclosed separately). Indicate whether or not additional scientific critique has been obtained.

The swine flu pandemic has failed to manifest itself on the scale that had been expected. Predicted numbers of swine flu cases were used to inform the design and methodology of the Painted project. To compensate for the greatly reduced number of cases presenting at hospital emergency departments (a reduction which compromises the study's ability to adequately test the predictive value of the various triage components) we propose extending the duration of the study by three months and to use that time to undertake a retrospective examination of emergency departments' attendances. The intention is to reconfigure the study along the lines of a case–control model. We will retrospectively identify additional positive cases, as defined in the protocol, and then add the new positive cases to those accrued prospectively. Negative cases in the data set then act as the 'controls'. Statistical commentary on the reconfiguration is presented in the revised version of the protocol (on pages five and six).

The project funder (the National Institute for Health Research) has approved the extension of the project.

Any other relevant information

Applicants may indicate any specific ethical issues relating to the amendment, on which the opinion of the REC is sought.

We do not propose to inform the retrospectively identified positive cases that we are using their routinely available data. Our reasoning is as follows. By definition these patients will have been critically ill (or they would not be positive cases) and of these some will have died. But it is not possible for us to reliably identify those who have fully recovered or those who have not. Further, this process of retrospectively identifying an individual as a potential positive case for Painted is occurring some months after the original infection event. Thus there is uncertainty over the final outcome for the patients concerned and a considerable time delay in identifying them. Given this uncertainty and delay we feel that attempts to inform these individuals will run the risk of causing such confusion and distress as to outweigh any potential ethical benefit that might otherwise have been gained.

List of enclosed documents

Document	*Version*	*Date*
Protocol	5	January 2010

Declaration

I confirm that the information in this form is accurate to the best of my knowledge and I take full responsibility for it.

I consider that it would be reasonable for the proposed amendment to be implemented.

Signature of Chief Investigator: ……

Print name: Professor Steve Goodacre

Date of submission: 29 January 2010

Appendix 7
Response from NIGB

12 February 2010

Re: Application to Ethics and Confidentiality Committee for section 251 support – Emergency department triage methods for suspected pandemic influenza

Thank you for the revised study protocol for section 251 support to access patient identifiable data without consent.

Members have considered the revised protocol and due to the issues raised, requested that a new application be submitted to the next Ethics and Confidentiality Committee (ECC) meeting taking place in March. Members agreed that this application would not be suitable to be considered under the fast track procedure for the following reasons:

1. The previous application was given fast track approval at a time when there was a real urgency to have the application considered due to the level of risk which the pandemic influenza A/H1N1 2009 may have presented.
2. The pandemic influenza did not turn out to be as widespread as expected and this has implications on considerations within this new request for section 251 approval.
3. The proposed changes to the study appear to be a complete change of study methodology with a new retrospective arm.

Please explicitly consider and address the following in your submitted application:

1. The ECC position on retrospective studies of relatively small numbers of patients is that consent should be sought via the members of the direct clinical care team involved in the care and treatment of the individual cohort. If consent is not feasible, data extraction from the clinical record should be carried out by the direct clinical care team and only fully anonymised data returned to the researchers.
2. If consent is to be sought from the living cohort as described above then section 251 approval would not be required. If consent is considered to be impracticable then the section 251 application must provide strong justification as to why consent cannot be sought.
3. Similarly, justification should be provided in relation to those patients who are deceased and consent from the family cannot be obtained. Please note a clear differentiation is needed in the application between patients who are still alive and those that are deceased.
4. Please note that the deadline for submitting a fully completed application is **26 February 2010.** Please ensure all required documents are submitted along with the application. A list of the documents can be found here.

If you have any queries please do not hesitate to contact me on 020 7633 7021.

Appendix 8
Response from REC

NHS

National Research Ethics Service

North West 5 Research Ethics Committee - Haydock Park

North West Centre for Research Ethics Committees
3rd Floor - Barlow House
4 Minshull Street
Manchester
M1 3DZ

Tel: 0161 625 7819
Fax: 0161 237 9427

26 February 2010

Professor Steve Goodacre
Health Services Research
ScHARR
University of Sheffield
Regent Court
30 Regent Street
Sheffield S1 4DA

Dear Professor Goodacre

Study title:	**Evaluation and development of triage methods used to select patients with suspected pandemic influenza for hospital admission**
REC reference:	**09/H1010/60**
Amendment number:	**2, 29th January 2010**
Amendment date:	**29 January 2010**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review decided that they could not give a favourable ethical opinion of the amendment, for the following reasons:

The swine flu pandemic has failed to manifest itself on the scale that had been expected. The predicted numbers of swine flu cases were used to inform the design and methodology of the study. To compensate for the greatly reduced number of cases presenting at hospital emergency departments' the amendment (Amendment 2; 29th January 2010) sought approval for a three month extension to the study and to undertake a retrospective examination of emergency departments' attendances in order to reconfigure the study along the lines of a case-control model. It is intended to retrospectively identify additional positive cases and add new positive cases to those accrued prospectively. Negative cases in the dataset will then act as the 'controls'. It is not proposed to inform patients who have been retrospectively identified as positive cases that the research team intends to use their data.

A revised protocol (version 5 dated 29 January 2010) had been submitted in support of the amendment.

The Sub-Committee expressed the following concern with the proposed amendment as follows:-

A. It was noted that the study had received approval from the National Information Governance Board for Health and Social Care (NIGB) to process identifiable patient data without consent (under section 251 of the NHS Act 2006). It was further noted that the proposed amendment had also been submitted to the NIGB for approval. Thus the REC sought written confirmation that the NIGB approval to process identifiable patient data without consent had been extended to include patients who have been retrospectively identified as positive cases. Ethical approval for the amendment will not be issued until such time as notification of NIGB approval is received.

B. Leading on from the above, the Sub-Committee questioned the rationale underpinning the proposal not to inform patients that their data would be used in research without consent, i.e. because it was not possible to reliably identify those who had fully recovered or those who had died. Specifically, if in the first instance it was possible to identify (presumably via NHS numbers?) retrospective cases from the examination of emergency department attendances, why was it not also possible to use NHS numbers to identify patients who had died? This would presumably enable reliable identification of patients who had subsequently recovered in order to seek informed consent to use their data.

In conclusion should Amendment 2 dated 29th January 2010 fail to obtain NIGB approval then the REC would expect the research team to fully address the issues which have been raised in point B above.

In light of the request for NIGB approval as outlined above, the REC had no option but to reject the proposed amendment.

We regret to inform you that the amendment is therefore not approved. The study should continue in accordance with the documentation previously approved by the Committee.

Modifying the amendment

You may modify or adapt the amendment, taking into account the Committee's concerns. Modified amendments should be submitted on the standard Notice of Amendment form. The form should indicate that it is a modification of the above amendment. Please ensure that you submit all of the documents again that need to be reviewed, that is any of those listed below which are still relevant, as well as any revised or new documents.

A revised Notice of Amendment form must be submitted at least 14 days before you plan to implement the amendment. The Committee will then have 14 days from the date of receiving the notice in which to notify you that the amendment is rejected, otherwise the amendment may be implemented.

Documents reviewed

The documents reviewed at the meeting were:

Document	Version	Date
Covering Letter: From Richard Wilson, Project Manager		02 February 2010
Notice of Substantial Amendment (non-CTIMPs): 2, 29th January 2010		29 January 2010
Protocol	5	29 January 2010

Membership of the Committee

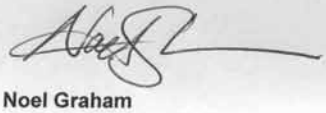
The members of the Committee who took part in the review at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

09/H1010/60:	**Please quote this number on all correspondence**

Yours sincerely



Noel Graham
Committee Co-ordinator

E-mail: noel.graham@northwest.nhs.uk

Enclosures: List of names and professions of members who took part in the review

Copies to:

Mr R Hudson
Research Office
The University of Sheffield
SHEFFIELD
S10 2TN

Mr R Wilson
Project Manager
The PaInTED Study
Health Services Research Section
ScHARR University of Sheffield
Regent Court
Regent Street
SHEFFIELD S1 4DA

R&D office for NHS care organisation at lead site: -

Ms G McVey
Sheffield Teaching Hospitals NHS Foundation Trust
Research Department
1st Floor
11 Broomfield Road
SHEFFIELD
S10 2SE

North West 5 Research Ethics Committee - Haydock Park

List of names and professions of members who took part in the review

Name	*Profession*	*Capacity*
Dr Donal Manning (Chair)	Consultant Paediatrician	Expert
Dr Tim Sprosen (Vice-Chair)	Chief Scientific Officer – UK Biobank and Medical Researcher/Epidemiologist	Expert
Professor Elizabeth Perkins	Director of The Health and Community Care Research Unit – The University of Liverpool	Lay

Appendix 9

Chief investigator reply to NIGB

Re: Application to Ethics and Confidentiality Committee for section 251 support Emergency department triage methods for suspected pandemic influenza

Thank you for your letter of 12 February 2010 and for considering the revised protocol for this study. We will not be submitting a new application to the next Ethics and Confidentiality Committee (ECC) meeting but will instead complete the project according to the original protocol. Unfortunately, based on the information outlined in your letter, it is apparent that we will not be able to undertake a meaningful study with section 251 support using the proposed case–control methodology.

The ECC position, as outlined in your letter, is that consent should be sought via the members of the direct clinical care team involved in the care and treatment of the individual cohort, and apparently that consent should be sought from the family of those who are deceased. We have some ethical concerns about contacting recently bereaved family members but there are no insurmountable barriers to seeking consent, so we cannot claim this is not feasible. However, we would anticipate that a substantial proportion of patients or relatives would not respond to our request for consent and subsequent responder bias would render the findings of the study worthless, or at least of such limited value as to not justify the expense of the project or intrusion into patients and relatives lives.

Even if the ECC could be persuaded to alter its position on this issue we would not be able to complete the project in the timeframe required. We do not have funding available to extend staff contracts while considerations continue and would therefore have no staff available to complete the project work by the time section 251 support for the revised protocol were in place. Furthermore, clinical staff in the participating hospitals have informed us that they are neither willing nor able to commit time to extract data from the clinical records as they already have a heavy burden of clinical commitments.

We would be grateful if our comments could be fed back to the ECC.

Appendix 10
Study protocol

Research objectives

1. To determine the discriminant value of currently available emergency department triage methods for predicting severe illness or death in patients presenting with suspected pandemic influenza.
2. To determine the independent predictive value of presenting clinical characteristics and routine tests for severe illness or death in patients presenting with suspected pandemic influenza.
3. To determine whether the discriminant value of emergency department triage can be improved by developing two new triage methods based upon (1) presenting clinical characteristics alone and (2) presenting clinical characteristics, electrocardiogram (ECG), chest X-ray and routine blood test results.

Existing research

The United Kingdom (UK) influenza pandemic contingency plan predicts around 750,000 excess emergency department attendances and 82,500 excess hospitalisations during a pandemic.[1] Given that there is likely to be significant staff absence it will be impractical for all patients fully to be assessed by a senior clinician. If, as is likely, interpandemic levels of care cannot be offered during a pandemic, methods of triage and resource allocation will have to be fair, robust and reproducible.[2]

The term triage is often used to describe a brief initial assessment in the emergency department to determine patient order of priority in the queue to be seen. In this proposal we use the term triage more broadly to include the full process of emergency department assessment, potentially including investigations such as blood tests and X-rays, and apply it to decision-making regarding whether the patient should be admitted and whether they should be referred for high dependency or intensive care.

Emergency department triage methods need to accurately predict the individual patient's risk of death or severe illness. The predicted risk can then guide decision-making. Patients with a low risk may be discharged home, those with a high risk admitted to hospital, and those with a very high risk referred for high dependency or intensive care. The level of risk used to trigger these decisions need not necessarily be fixed or determined in advance. Indeed, it is likely that decision-making thresholds could change during the course of a pandemic as the balance between resource availability and demand changes. Triage methods that use a risk prediction score to determine the need for hospital care may therefore be more useful than a triage rule that classifies patients into admission and discharge categories.

Current Health Protection Agency (HPA) guidance, supported by the British Thoracic Society and British Infection Society, recommends the use of the CURB-65 pneumonia score.[3] This score uses five variables (confusion, urea level, respiratory rate, blood pressure and age) to generate a score between zero and five. More recent Department of Health guidelines on surge capacity in a pandemic also considered use of a physiological–social score [Pandemic Modified Early Warning Score (PMEWS)].[4] This score uses physiological variables, age, social factors, chronic disease and performance status to generate a score between zero and seven. The most recent national guidance, specific to H1N1 (swine), includes a new swine flu hospital pathway for emergency department management with seven criteria, any one of which predicts increased risk and the need for hospital assessment.[5]

Existing literature shows CURB-65 to perform reasonably well as a mortality predictor in an emergency department population with community-acquired pneumonia [area under the receiver–operator Curve (AUROC) 0.76],[6] but less well in predicting the need for high-level care (AUROC 0.69[7] and 0.64[8]). The physiological–social score considered by the Department of Health (PMEWS) is not a particularly good mortality predictor in community-acquired pneumonia (used as a proxy for pandemic influenza), with an AUROC score of 0.66, but performed much better predicting requirement for higher-level care (AUROC 0.83)[8] and has shown promise when used in the prehospital setting to determine need

for emergency department attendance [AUROC 0.71[9] and 0.8 (J Grey, February 2009, personal communication)]. The most recently issued national guidelines appear to have been developed by expert consensus and have as yet undergone no validation in the appropriate patient populations.

To our knowledge there have been no studies evaluating any of these triage methods in patients with suspected pandemic influenza and no studies to develop a risk prediction score in the emergency department population with suspected pandemic influenza.

We are not aware of any studies currently planned or under way to test or develop emergency department triage methods in the current pandemic. The Intensive Care National Audit and Research Centre (ICNARC) have been commissioned to undertake a swine flu triage project (SwiFT) for admitted patients referred to critical care. SwiFT involves modelling to identify which of those patients who would usually be admitted to critical care may be refused admission at the height of the pandemic (once all surge capacity measures have been instituted) – i.e. both those with a very high likelihood of death despite critical care and those that may be expected to survive without critical care.

Our project and SwiFT will be examining different triage decisions and different patient groups and are clearly separate projects. We will be collaborating with INCARC to ensure that our research is synergistic and does not involve any unnecessary duplication of work.

Research methods

We will undertake a prospective cohort study of patients presenting to the emergency department with suspected pandemic influenza. Emergency department staff will be provided with a standardised form for assessing such cases that will double as clinical notes and study data collection form. It will include the elements of the CURB-65 score, the physiological–social score, the swine flu hospital pathway and any other measures that could be routinely recorded in the emergency department (comorbidities, physiological observations, routine blood tests, ECG and chest X-ray). We will also record details of any prepresentation antiviral medication, antibiotics and immunisation status (once available). Research staff will then follow patients up until 30 days after attendance by hospital record review and, if appropriate, general practitioner contact to identify patient outcomes.

Planned intervention

We will evaluate triage methods used to determine whether a patient with suspected pandemic influenza should be admitted to hospital or not, and whether they should be admitted to intensive or high dependency care. These will include the CURB-65 score, the physiological–social score and the swine flu hospital pathway. We will also develop two new triage methods based upon (1) presenting clinical characteristics alone and (2) presenting clinical characteristics, ECG, chest X-ray and routine blood test results.

The first score will only use variables available at initial patient assessment, i.e. history and examination, including simple technologies such as automated blood pressure measurement and pulse oximetry. This triage method can be used to assess patients for the need for hospital investigation and identify patients that can be discharged without further assessment. It could potentially be used, with appropriate validation, to assess patients in the community.

The second triage method will be based upon all available emergency department data, including routine blood tests, ECG and chest X-ray findings. This triage method can be used for two potential purposes: (1) identification of patients with a low risk of adverse outcome who can be discharged home after emergency department assessment, and (2) identification of high-risk patients who are likely to need high dependency or intensive care.

We will evaluate the ability of each method to predict whether patients die or require respiratory, cardiac or renal support. We will not evaluate the impact of triage methods upon patient care. Intervention in the study will therefore only consist of data collection and follow-up. Patient management will continue according to current Department of Health guidance.

Planned inclusion/exclusion criteria

We will include all adults and children presenting the emergency department of the participating hospitals with suspected pandemic influenza during the peak of the pandemic. Patients will be eligible for inclusion if they meet the current clinical diagnostic criteria of (1) fever (pyrexia ≥ 38°C) or

a history of fever and (2) influenza-like illness (two or more of cough, sore throat, rhinorrhoea, limb or joint pain, headache, vomiting or diarrhoea) or severe and/or life-threatening illness suggestive of an infectious process, or if they meet any future clinical diagnostic criteria recommended by the Department of Health. The assessing clinician will determine eligibility and complete the data collection form if the patient is considered to have suspected pandemic influenza. We will not attempt to retrospectively apply the clinical diagnostic criteria and exclude patients who appear to have been inappropriately included. Patients will only be excluded if they request exclusion from the study.

Ethical arrangements

We are seeking fast track Research Ethics Committee (REC) and National Information Governance Board (NIGB) approval. Application forms for both are completed and ready to send as soon as a funding decision is made.

Risks and anticipated benefits for trial participants and society

The study will not alter patient management and will simply collect routinely available data at presentation and follow-up. No additional diagnostic tests will be performed. The risks to patients involved in the study are therefore very low and principally relate to data protection and confidentiality.

Data will be abstracted from the collection form and hospital notes by researchers working with an honorary contract from the hospital Trust or researcher passport recognised by the Trust. This researcher will keep a record of all patients who withdraw from the project but will not communicate details to other staff. He/she will enter anonymised data onto a secure online database provided by the Clinical Trials Unit at the University of Sheffield. The research team in general will only have access to anonymised data on the secure database.

Patients involved in the study will potentially benefit from the use of the standardised patient assessment form. This will ensure that important variables are recorded and communicated between staff providing care. The standardised form can also be used to remind staff of current guidance for management.

Future patients with suspected pandemic influenza and society in general will benefit from evaluation and development of accurate triage methods that have the potential to improve clinical decision-making and ensure that patients receive the right care and health service resources are optimally used.

Informing potential trial participants of possible benefits and known risks

Posters in all participating departments will be prominently displayed advising patients of the project and providing contact details for further information. Information leaflets will be available that briefly describe the nature and purpose of the study and provides contact details for further information.

Obtaining informed consent from participants

We will not be seeking patient consent to participate on the basis that the study is limited to collection of routinely available data and any delays in patient assessment would risk compromising patient care. The information leaflet outlined above will provide a tear-off slip with contact details that patients can use to inform the hospital or research team if they wish to withdraw from the study. Patients who wish to withdraw from the study will have their study records deleted. Their decision to withdraw will not be communicated to clinical staff providing further care and will not influence their subsequent management.

Proposed time period for retention of relevant study documentation

The original data collection form will constitute the clinical notes and be kept in each hospital according to normal practice. A copy of the data collection form will be retained by the researcher in a secure location in each hospital. These will be destroyed 6 months after the end of the project. The anonymised database will be maintained by the Clinical Trials Unit until 10 years after the end of the project.

Proposed sample size

The sample size will ultimately depend upon the size and severity of the pandemic, but combining

our data collection method with clinical case documentation will ensure that data are collected for most cases. We plan to collect data during the pandemic at four hospitals in Sheffield and Manchester, covering a population of over 1 million. We are piloting data collection now so that it can start as soon as funding is approved and ethical and regulatory requirements are satisfied.

Department of Health estimates of a 25% clinical attack rate and illustrative case hospitalisation and case fatality rates of 0.55% and 0.37%, respectively, suggest that a pandemic may lead to 12,500 emergency department attendances, 1400 hospitalisations and 900 excess deaths in our population.[1] If half of these occur while we are collecting data then around 6000 cases with 600 positive outcomes will be available for analysis.

We will split the database for analysis into two data sets of equal size, one for developing new scores and testing existing scores, and one for comparing the new and existing scores. To develop a new triage method we need around 10 events per parameter tested in the model, so 200 positive cases would allow us to test 20 parameters. A sample size of 283 positive cases ensures a power of 80% to compare an AUROC curve of 0.85 versus 0.90 at 5% significance, assuming a correlation of 0.6 between scores.[10]

Statistical analysis

Existing triage methods

CURB-65, the physiological-social score and the swine flu clinical pathway will be assessed by calculating the AUROC (*C*-statistic) for discriminating between cases with and without a positive outcome (defined as death or need for support of respiratory, cardiovascular or renal function) and sensitivity and specificity at key decision-making thresholds.

New triage methods

As outlined above, we will develop two new triage scores: one based on initial assessment only and the other based on all emergency department data. We will test the association of each potential clinical predictor variable with outcome and then undertake logistic regression to identify independent predictors of outcome. The strongest independent predictors of outcome will then be combined to form a new triage score. Continuous predictor variables will be divided into categories on the basis of the relationship of the variable with outcome. Integer weights will be assigned to each category of predictor variable according to the coefficient derived from a multivariate model using categorised independent predictors. This will generate a composite clinical score in which risk of positive outcome increases with the total score.

The data set will be split randomly into two equal sets. The first set will be used to compare the *C*-statistic of existing scores and derive the two new scores. The second set will be used to compare the *C*-statistic of the two new scores to that of the best existing score.

Proposed outcome measures

Patients will be followed up by researcher review of case note and hospital computer record review up to 30 days after emergency department presentation. If they die or require respiratory, cardiovascular or renal support they will be defined as having a positive outcome. If they survive to 30 days without requiring respiratory, cardiovascular or renal support they will be defined as having a negative outcome. If a severe pandemic leads to hospital resources being overwhelmed we will categorise patients as having a positive outcome if they were deemed to have needed respiratory, cardiovascular or renal support but were denied this due to lack of resources. We will also record whether they are treated with antiviral agents or antibiotics, and the length and location of any hospital stay.

Respiratory support is defined as any intervention to protect the patient's airway or assist their ventilation, including non-invasive ventilation or acute administration of continuous positive airway pressure. It does not include supplemental oxygen alone or nebulised bronchodilators. Cardiovascular support is defined as any intervention to maintain organ perfusion, such as inotropic drugs, or invasively monitor cardiovascular status, such as central venous pressure or pulmonary artery pressure monitoring, or arterial blood pressure monitoring. It does not include peripheral intravenous cannulation and/or fluid administration. Renal support is defined as any intervention to assist renal function, such as haemoperfusion, haemodialysis or peritoneal dialysis. It does not include intravenous fluid administration.

Outcome assessment will be based primarily on researcher review of hospital computer records and case notes. If there is no evidence in these of a positive outcome the patient will be recorded as

having a negative outcome. If outcome is uncertain (for example, if the patient is transferred to another hospital or leaves hospital against medical advice) the researcher will contact the patient's general practitioner for clarification. This means that there will be a small risk of misclassification if the patient dies or attends another hospital after discharge home, but we believe the resource implications of attempting to identify such cases does not justify the small potential risk of bias.

We have selected an outcome measure that has a relatively clear definition and unequivocally indicates a case in which hospital admission and high-dependency care would be desirable. The disadvantage of this definition is that it excludes patients who might benefit from other aspects of hospitalisation, such as oxygen supplementation or intravenous fluids. However, oxygen and intravenous fluids are often administered to patients with little clinical need for these treatments, administration is often poorly recorded and administration may be based on the clinical variables being tested in this project rather than objective clinical need. Including these treatments in our definitions of respiratory or cardiovascular support would thus carry a substantial risk of overestimating the prevalence of serious outcome and of overestimating the association between predictor variables and outcome.

We will also not attempt to determine whether deaths were likely to be amenable to treatment and will thus not explore the issue of whether treatment would be futile. It is possible that a severe pandemic could result in a need to identify cases where treatment would be futile, but this is beyond the scope, and possibly incompatible with the aims, of this proposal.

Research governance

The University of Sheffield will be the study sponsor. The project management group (PMG), consisting of the coapplicants and the appointed research staff, will manage the study. The PMG will meet monthly by teleconference or in person to oversee study progress.

Time constraints mean that we will not be able to convene a formal steering committee to review the protocol, meet regularly and fulfil all the normal functions. However, we will ask an independent statistician, clinician and layperson to form a steering committee that will provide independent advice and monitor progress by email or telephone.

Project timetable and milestones

We have already prepared ethics and NIGB applications, and are currently piloting the data collection forms. We will be able to start the project as soon as a funding decision is made. Research staff have been identified and can start work on the project at short notice.

	Aug	Sep	Oct	Nov	Dec	Jan
Processes						
Ethics, NIGB and governance	×					
Data collection		×	×	×		
Follow-up			×	×	×	
Data analysis					×	×
Reporting and dissemination						×
Staffing						
Project manager	×	×	×	×	×	×
Clerical assistant	×	×	×	×	×	×
Database manager	×	×	×	×	×	
Researchers		×	×	×	×	

Expertise

The research team combines the leading experts on emergency management of suspected pandemic influenza (KC, DW and AB) with the statistical expertise and research infrastructure of the Medical Care Research Unit (SG, JN, MC and RW). We also have public health input from MS who is currently on secondment with the HPA.

The proposal builds on an existing collaboration developed as part of the Medical Research Council (MRC)-funded DAVROS Study (Development and validation of risk-adjusted outcomes for systems of emergency care). For the DAVROS Study we have collected presenting data from over 10,000 patients admitted to hospital with a medical emergency and then followed them up to determine their 30-day outcomes. This has involved establishing processes for using routine data without patient consent, including data management and data protection, which have been approved by the REC and NIGB, and used effectively without significant problems. DAVROS was undertaken to develop a

risk-adjustment method but is now also being used by KC, SG and JN to develop a clinical triage tool for emergency medical admissions. Our proposal will apply the data collection and analysis methods used in DAVROS to the specific problem of suspected pandemic influenza.

David Harrison, from ICNARC, has agreed to be a collaborator on the project. He is currently working with us on the DAVROS study. We will draw upon his expertise in risk prediction and ensure that our project works synergistically alongside pandemic influenza research currently being undertaken by ICNARC.

Specific details of the collaborating units

Medical Care Research Unit, Sheffield

Steve Goodacre and Jon Nicholl have undertaken many major national evaluations in emergency care, including development of clinical prediction methods. Current projects provide the necessary infrastructure to rapidly undertake the proposed research. Richard Wilson is currently managing the DAVROS study and has developed extensive expertise in data collection, management and protection in observation studies using routine data sources without patient consent.

University Hospital of South Manchester NHS Trust

Kirsty Challen and Darren Walter are emergency physicians and Andrew Bentley is an accredited critical care and respiratory physician. They have previously evaluated triage methods for pandemic influenza and are leading experts in this field.

Department of Public Health, Sheffield

Mark Strong is a public health specialist who is currently on secondment with the HPA.

Sheffield Clinical Trials Unit

Mike Campbell is an experienced medical statistician with expertise in development and validation of clinical prediction rules.

Service users

Enid Hirst has agreed to be the patient/public representative for the project and has reviewed the proposal. She has acted as a user representative for many previous health service research projects undertaken by our group, including being a lay member of the Steering Committee of the DAVROS study.

Enid previously spent 8 years with Sheffield Community Health Council, was a lay member of the Steering Committee for NHS Direct Yorkshire and Humber, was a member of Unscheduled Care Network Board in Sheffield, spent 3 years with Sheffield Children's Hospital Patient Forum, and has attended Trust Board meetings at Sheffield Children's Hospital for many years as an observer for the Community Health Council and then the Patient Forum. She is now a member of Sheffield LINk (Local Involvement Network), a lay member of the Out of Hours Accreditation Group, is on the Dental Services Joint Planning Group for Sheffield, is a patient representative for the Group looking into Dentally Anxious Patients, and is a patient representative on the new Critical Care/Emergency Medicine Priority Group.

Her role will include the following:

1. reviewing the protocol and specifically advising on ethical issues and arrangements for data protection and confidentiality
2. reviewing the poster and information leaflet
3. patient/public representation on the steering committee
4. lay input into reporting and dissemination of findings.

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