PAINTED

The PAINTED study: PAndemic INfluenza Triage in the Emergency Department

Professor Steve Goodacre
School of Health and Related Research (ScHARR)
30 Regent Street
Sheffield
S1 4DA

Tel: (+44) (0)114 222 0842
Fax: (+44) (0)114 222 0749

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Planned investigation:

Research objectives
We aim to identify the most accurate triage method for predicting severe illness among patients attending the emergency department with suspected pandemic influenza.

Our specific objectives are:
1. To determine the discriminant value of emergency department triage methods for predicting severe illness in patients presenting with suspected pandemic influenza
2. To determine the discriminant value of presenting clinical characteristics and routine tests for identifying severe illness
3. To determine the independent predictive value of presenting clinical characteristics and routine tests for severe illness
4. To develop two new triage methods based upon (a) presenting clinical characteristics alone and (b) presenting clinical characteristics, electrocardiogram (ECG), chest X-ray and routine blood test results

Existing research
Prior to the 2009 H1N1 pandemic, the United Kingdom (UK) influenza pandemic contingency plan predicted around 750,000 excess emergency department attendances and 82,500 excess hospitalisations during a pandemic [1]. A recent consultation document suggested that a pandemic could result in 50% of population having some symptoms, of whom 30% would seek primary care and 1-4% would need hospital admission [2]. The Pandemic Influenza Advisory Committee Subgroup on Modelling have estimated a likely clinical attack rate of 3-35% (worst case scenario 50%), with 10-25% of these to have complications and a peak demand in the worst case scenario of 13% of the population being ill [3].

Pandemic planning needs to encompass a wide range of potential scenarios, but even projections at the less severe end of the spectrum could cause substantial problems of overcrowding at emergency departments that are already often working close to capacity. Methods of triage for patients presenting to the emergency department with suspected pandemic influenza are therefore required and need to be fair, robust and reproducible [4].

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.

Health Protection Agency (HPA) guidance prior to the 2009 pandemic, supported by the British Thoracic Society and British Infection Society, recommended the use of the CURB-65 pneumonia score [5] for patients with suspected influenza-related pneumonia. This score uses five variables (confusion, urea level, respiratory rate, blood pressure and age) to generate a score between zero and five. Subsequent Department of Health guidelines on surge capacity in a pandemic also considered use of a physiological-social score (Pandemic Modified Early Warning Score (PMEMS)) [6]. This score uses physiological variables, age, social factors, chronic disease and performance status to generate a score between zero and seven. National guidance specific to the 2009 H1N1 pandemic included a swine flu hospital pathway for emergency department management with seven criteria, any one of which predicts increased risk and the need for hospital assessment [7].

We used the autumn/winter phase of the 2009 H1N1 pandemic in Sheffield and Manchester to evaluate the discriminant value of three potential systems for triage of pandemic influenza patients in the emergency department: CURB-65, PMEWS and the swine flu hospital pathway [8,9]. However, the pandemic in these areas was less severe than predicted and only five patients of the cohort of 481 met our predefined criteria for critical illness. Within this cohort the discriminant value (c-statistic) of the three systems for predicting critical illness was moderate (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)). Their performance in predicting hospital admission was worse: CURB-65 0.65 (95% CI, 0.54 to 0.76), PMEWS 0.76 (0.66 to 0.86) and the swine flu hospital pathway 0.62 (0.51 to 0.72). These findings suggested that clinicians were not using the recommended triage methods when deciding whether to admit or discharge patients, and raised concerns about the accuracy of these methods for predicting adverse outcome.

Other research during the pandemic cast doubt on the utility of existing triage systems. The SwiFT study of patients admitted to critical care with H1N1 found 68% scored 0 or 1 using CURB-65 (i.e. recommended for hospital discharge)[10]. This is supported in evidence from a Canadian seasonal flu cohort, where no triage system performed well in predicting intensive care admission (c-statistics PMEWS 0.63 (0.57-0.69), CURB-65 0.58 (0.52-0.64)[11]. The best discriminator in this cohort was SMART-COP, a system specifically developed to predict intensive care admission in community-acquired pneumonia [12] which achieved a c-statistic of 0.73 (0.67-0.79) but has not to our knowledge been examined in a pandemic cohort. The SwiFT study [10] also developed a new score based on systolic blood pressure, temperature, heart rate, respiratory rate, neurological status and inspired oxygen concentration to predict adverse outcome. The SMART-COP and SwiFT scores therefore offer alternative triage methods that require validation in a pandemic. We are not aware of any other new scores to emerge since the 2009 pandemic.
In addition to our study and SwiFT, a number of cohort studies were undertaken during the 2009 H1N1 pandemic to identify risk factors for poor outcome in various groups. We have systematically reviewed these studies and present the main findings in the appendix of this project description. The predominant predictors of adverse outcome were chronic co-morbidities and obesity [13-18] with conflicting evidence regarding the risk of pregnancy [10,15]. Acute physiological disturbances, particularly hypoxia, were also found to have prognostic value [10,14, 19-25].

The existing research therefore suggests that, although there are a number of patient characteristics and clinical measures that can predict adverse outcome, the available data do not support the use of any specific triage methods in suspected pandemic influenza.

Research methods
We plan to undertake a prospective observational cohort study of patients attending the emergency department with suspected pandemic influenza to evaluate existing triage methods, identify clinical predictors of adverse outcome and develop new triage methods.

Predictor variable data collection
Emergency department staff will be provided with a standardised form for assessing patients with suspected influenza that will double as clinical notes and study data collection form. It will include the elements of all currently available triage methods, variables identified in previous studies as being predictors of adverse outcome (see appendix) and any other potential predictors that are routinely recorded in the emergency department (co-morbidities, physiological observations, routine blood tests, ECG and chest x-ray). We will also record details of any pre-presentation anti-viral medication, antibiotics and immunisation status.

Planned Interventions
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, PMEWS, the swine flu hospital pathway, SMART-COP, the SwiFT score and any new methods developed before the next pandemic. We will also develop two new triage methods based upon (a) presenting clinical characteristics alone and (b) presenting clinical characteristics, electrocardiogram (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 whatever Department of Health guidance is in place at the time of the pandemic.

We will initially aim to develop triage methods that can be applied to the whole population of patients presenting to the emergency department. Age dependent variables will be assessed and included in the triage method in relation to age specific normal ranges. We will then explore whether different triage methods may be appropriate for different patients, particularly whether a different triage method may be appropriate for children.

**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, rhinorrhea, 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.

**Proposed outcome measures**

Patients will then be followed-up until 30 days after attendance by hospital record review. Patients who die or require respiratory, cardiovascular or renal support they will be defined as having an adverse outcome. If they survive to 30 days without requiring respiratory, cardiovascular or renal support they will be defined as having no adverse outcome. If a severe pandemic leads to hospital resources being overwhelmed we will categorise patients as having an adverse 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. At day 30 the anonymous data will be entered into the database.

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 canulation 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 research nurse review of hospital computer records and case notes. The hospital computer records will be checked at least 30 days after presentation. If the patient is alive at 30 days, was discharged home from the emergency department and did not reattend hospital, they will be recorded as having no adverse outcome. If they died, were admitted to hospital or reattended hospital within 30 days, their hospital notes will be retrieved and reviewed by the research nurse. If there is no evidence in the hospital notes of an adverse outcome the patient will be recorded as having no adverse outcome. If outcome is uncertain (for example, if the patient is transferred to another hospital or leaves hospital against medical advice) this will be recorded as no adverse outcome. 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 over-estimating the prevalence of serious outcome and of over-estimating 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.

**Proposed sample size**
The sample size will ultimately depend upon the size and severity of the pandemic. Our pragmatic data collection methods will ensure that we maximise any opportunity to evaluate emergency department triage methods in a pandemic.

Our experience in the 2009 pandemic has shown us that pre-pandemic estimates of case hospitalisation and case fatality rates can be very misleading and that sample size estimates must take into account considerable uncertainty in these estimates. Nevertheless, we have also shown that informative findings can be generated even in a pandemic with a very low rate of adverse outcome.
Given that most cases of suspected pandemic influenza (even in a severe pandemic) do not result in an adverse outcome, the key variable in determining study power is the number of cases with an adverse outcome. A single cohort including at least 150 cases with adverse outcome would allow us to estimate the c-statistic of a triage method, clinical variable or test with a standard error of 0.03 (assuming the true c-statistic was 0.8). The table below shows the standard error resulting from samples with smaller numbers of adverse outcomes.

<table>
<thead>
<tr>
<th>N with adverse outcome</th>
<th>Standard error (assuming c-statistic was 0.8)</th>
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<tbody>
<tr>
<td>150</td>
<td>0.033</td>
</tr>
<tr>
<td>125</td>
<td>0.036</td>
</tr>
<tr>
<td>100</td>
<td>0.040</td>
</tr>
<tr>
<td>75</td>
<td>0.046</td>
</tr>
<tr>
<td>50</td>
<td>0.056</td>
</tr>
</tbody>
</table>

A sample with N=150 adverse outcome would estimate the sensitivity of a dichotomised rule, variable or test with a standard error as outlined in the table below, depending on the sensitivity at the threshold used. Estimates of specificity would obviously be very precise given the anticipated low prevalence of adverse outcome.

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Lower limit of 95% CI</th>
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<tbody>
<tr>
<td>1.00</td>
<td>0.98</td>
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<tr>
<td>0.95</td>
<td>0.90</td>
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<td>0.90</td>
<td>0.84</td>
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<td>0.85</td>
<td>0.78</td>
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<tr>
<td>0.80</td>
<td>0.73</td>
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The same cohort could be used to identify independent predictors of outcome and develop new triage methods (objectives 3 and 4). The number of variables that could be tested as independent predictors of outcome in a multivariable model and for inclusion in a triage method would depend upon the sample size. Based on the rule of thumb of needing at least 10 events for each independent regression variable in a logistic regression, a cohort with 150 cases with adverse outcome would allow us to test up to 15 parameters [26].

These estimates assume that each triage method and predictor variable will be used and tested on the whole cohort. However, we plan to explore whether different patients require different triage methods, particularly whether a different triage method is required for children and adults. Data from the 2009 H1N1 pandemic suggest that around a quarter to a third of adverse outcomes may occur in children [14,33]. To increase the probability that we will have at least 50 cases with adverse outcome among children we will aim to recruit a total of 200 cases with adverse outcome rather than 150.

If we assume that the prevalence of adverse outcome is the same as our 2009 cohort (1%) then we would need to collect data from 20,000 cases to identify 200 with an adverse outcome. We have therefore used this estimate in planning, although it is likely to be an overestimate of the total numbers required given the mild nature of the 2009 pandemic. A
more severe pandemic would allow more precise estimates to be made with no additional costs or would allow us to reduce the total number of cases required to identify 200 with an adverse outcome.

If we are able to develop a new triage method that appears to have superior discriminant value to existing methods then we would want to validate this method in a new cohort. A sample including 421 cases with adverse outcome would provide 80% power 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. We have not included validation of a new triage method in our objectives because this would require (a) successful development of a new method and (b) a much larger sample size, with associated costs and assumptions about pandemic severity. However, if the pandemic is severe (i.e. the prevalence of adverse outcome exceeds 3%, so the number with adverse outcome exceeds 450) we will split the cohort into two equal cohorts to allow testing of existing rules and derivation of new rules on one half and validation of new rules, with comparison to existing rules, on the other.

We plan to collect data across 40 hospitals and have based our sample size calculation on the assumption of receiving 500 completed forms, including an average of 5 adverse outcomes, per hospital over the course of the pandemic.

**Statistical analysis**

In all analyses only age will be treated as a continuous variable (with possible reparameterisation). All other continuous variables will be categorised on the basis of their use in existing risk scores or previous studies. This is because most continuous variables used in risk prediction have a non-linear association with adverse outcome, with increased risk at high and low values.

It is likely that a proportion of data for most predictor variables (especially blood results) will be missing. The most likely reason is that a measurement would not be made or test performed if it was expected to be normal. Missing data will therefore be handled in constructing scores and in multivariable analysis by assuming that all missing values are normal (i.e. score zero in the relevant risk score). A sensitivity analysis will be performed by imputing missing values and comparing results between the three scenarios of excluding cases with missing values, treating missing values as normal and using imputed values for missing values.

Existing triage methods will be assessed by calculating the area under the ROC curve (c-statistic) for discriminating between cases with and without an adverse outcome (defined as death or need for support of respiratory, cardiovascular or renal function) and sensitivity and specificity at key decision-making thresholds.

The discriminant value of each clinical variable or test for adverse outcome will be assessed by calculating the c-statistic and, for dichotomous variables, the sensitivity and specificity.

Independent predictors of outcome will be identified by entering all clinical variables with an association with outcome (p<0.2) into a multivariate logistic regression model.
New triage methods will be developed by combining the independent predictors of outcome into two new triage scores: one based on clinical variables measured at initial assessment only and the other based on all clinical variables (including blood tests and x-rays) measured in the emergency department. 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.

To determine whether different clinical scores are required for adults and children we will derive separate scores for adults (age >=16) and children. If any variables are included in one and not in the other we will compare c-statistics separately in each age group for models with and without the relevant variable. We will also test whether the weights attached to each variable differ sufficiently to affect prediction. The outcome may be that models with different predictors and/or different weights are required for adults and children.

If the pandemic is severe enough to allow the cohort to be split into derivation and validation cohorts with sufficient numbers of adverse outcome we will compare new triage methods developed during the project to existing triage methods by calculating c-statistics and sensitivity/specificity at key decision-making thresholds in the second cohort.

Data management
Data will be collected by the clinical staff caring for the patient using a standardised clinical assessment form that will double as routine clinical record and research data collection form. Research nurses employed by each hospital (and funded by the Comprehensive Local Research Network) will identify patients with suspected influenza for whom the standardised form was completed. Once 30 days have passed from attendance the research nurse will check the hospital computer system for deaths or hospital admissions. If death or hospital admission has occurred (estimated 15% of cases) the research nurse will retrieve hospital notes to record details of any adverse events. Once complete the research nurse will enter anonymised data into a secure online database provided by the Sheffield Clinical Trials Research Unit (CTRU). Patient identifiable information will not be recorded onto the database.

Piloting the data collection form
Before the next pandemic we will pilot and develop the standardised clinical assessment form we used in the 2009 pandemic. We will ask staff at participating hospitals to use the form for routine assessment of patients with seasonal influenza during the winter of 2012-13. We will seek staff feedback to make the form as user-friendly as possible and to ensure that it serves dual needs of collecting relevant information for routine clinical records and the data required for our research. We will promote use of the form so that it becomes the routine clinical record for patients presenting to the participating hospitals with suspected influenza. Once the form is developed we will create a secure online database to ensure efficient data management. We will then test the use of the form in practice.

We will ensure that the software supporting form production and the database is flexible so that the form can be amended and updated at short notice and with minimum
inconvenience to clinical and research staff. During the pilot phase and at the point of activation of the full study (see below) we will update our literature review to identify any new triage methods or potentially useful predictors of adverse outcome.

**Activation of the full study**
The project will be activated if and when an influenza pandemic results in increased emergency department attendances with suspected influenza. Research staff will promote the use of the standardised data collection form, collect follow-up data and undertake data entry. We will update our literature review (as outlined above) and monitor reports from areas where the pandemic develops to identify any potentially new predictors of adverse outcome that may be unique to the emerging pandemic. If any potentially new predictors are identified we will cascade information to clinical staff and amend the clinical assessment form to ensure that they are systematically recorded.

**Ethical arrangements**
We will seek Research Ethics Committee (REC) approval prior to piloting and in advance of any pandemic. We will seek approval to activate the project in the event of a pandemic without a further REC review. Our previous similar project in the 2009 H1N1 pandemic was approved by the REC. The planned processes for informing patients of the project and managing data are very similar to those approved in our 2009 project. During the previous 2009 project patient identifiable information was taken to allow monitoring, data validation and GP contact. The National Information Governance Board (NIGB) gave section 251 approval to this use of identifiable patient data without consent. However the NIGB was unable to give approval to the use of patient identifiable information in the pilot phase of this project and will not be constituted to give approval for a future pandemic. We will therefore not be collecting identifiable details in the pilot phase, but will use the pilot phase to test whether the study can be undertaken without identifiable data. Having assessed the potential limitations incurred by inability to use identifiable details we will explore whether approval to use identifiable details during the pandemic phase should be sought from the appropriate competent body.

**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.

The standardised clinical assessment form will be used as both routine clinical record and data collection form to ensure that care is not delayed by unnecessary duplication of data recording. The pilot phase will be used to ensure that this form is fit for both purposes and acceptable to clinical staff. The research nurses will keep a record of all patients who withdraw from the project but will not communicate details to other staff. Only anonymous data will be entered into the database by the clinical staff and therefore no one outside of the hospital, including the research team at Sheffield, will have access to patient identifiable information.
Patients involved in the study will potentially benefit from the use of the standardised clinical 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 provided for staff to hand to patients with suspected pandemic influenza 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 seek 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. The anonymised database will be maintained by the Clinical Trials Unit until ten years after the end of the project.

**Proposed action to comply with 'The Medicines for Human Use (Clinical Trials) Regulations 2004'**
Not applicable – this is not a clinical trial.

**Research Governance**
Sheffield Teaching Hospitals NHS Foundation Trust will be the study sponsor and the project will be managed by the School of Health and Related Research (ScHARR) in the University of Sheffield. The Hospital Trust and University share a joint research office in Sheffield to facilitate management of collaborative projects such as this. The Project Management Group (PMG), consisting of the co-applicants and any appointed research staff, will manage the study. The PMG will meet prior, during and after the pilot phase. After that meetings will be held annually until a pandemic emerges and the project is activated. During the pandemic the PMG will meet at least monthly, either in person or by teleconference. The Sheffield CTRU will manage data entry, data management and provide data ready for analysis by Professor Campbell.
A Steering Committee will be formed to oversee study progress. This will consist of an independent Chair and at least three independent members (including a relevant clinician, statistician and public/patient representative), the Chief Investigator and the Project Manager.

Project timetable and milestones:
June 2012 to September 2012: REC submission, and seeking regulatory approvals from participating NHS Trusts.
October 2012 to January 2013: Piloting and development of clinical assessment form.
February 2013: Project put on hold until pandemic emerges (T0)
T0: Project activated
T0 to T0+3 months: Data collection from 20,000 cases, including 200 with an adverse outcome, across 40 hospitals (see sample size section for details)
T0+3 to T0+6 months: Analysis and reporting

Expertise:
The research team combines experts on emergency management of suspected pandemic influenza (KC, DW and AB) with expertise in paediatric emergency medicine (IM), critical care (AB) and public health (AL), and the statistical expertise and research infrastructure of the Sheffield Clinical Trials Unit (SG, MC and RW).

The Team collaborated on a similar previous project during the 2009 H1N1 pandemic (HTA09/84/66). This project was completed and reported despite difficulties caused by research governance procedures and the unexpectedly mild course of the pandemic.

Steve Goodacre was Chief Investigator for HTA09/84/66 and is lead applicant for this proposal. He has undertaken many major national evaluations in emergency care, including development of clinical prediction methods. His current projects provide the necessary infrastructure to rapidly undertake the proposed research. Richard Wilson managed the DAVROS study and has developed extensive expertise in data collection, management and protection in observation studies using routine data sources without patient consent. Mike Campbell is an experienced medical statistician with expertise in development and validation of clinical prediction rules. Andrew Lee is a Senior Clinical University Teacher in Public Health who has a research interest in emergency planning and is currently collaborating with SG, KC and DW on an NIHR Service Delivery and Organisation project involving scoping the emergency planning literature.

Kirsty Challen and Darren Walter are emergency physicians with research interests in pandemic influenza and emergency planning, 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. Ian Maconochie is a paediatric emergency physician who has evaluated paediatric early warning scores, the predictive value of clinical features in sick children and the management of febrile children.

Service Users:
Enid Hirst has agreed to be the patient/public representative for the project and has reviewed the proposal. She acted as patient and public representative for our project in the 2009 pandemic and was an independent member of the study Steering Committee.

Enid is a founder member of the Sheffield Emergency Care Forum. This is a patient and public representative group with a specific interest in emergency care research. The Forum has reviewed this proposal and provided feedback. Enid will continue to provide a link between the project and the Forum.

Enid previously spent eight 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 three 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 LiNks (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
5. Liaison between the project and the Sheffield Emergency Care Forum

Justification of support required:
The exact timing of support required for the project will depend upon the timing of any pandemic. For the purposes of estimating costs we have assumed that the project will take place between 1 June 2012 and 31 May 2014, with the pilot taking place in autumn 2012 and the pandemic in autumn 2013.

The costs of existing staff are spread over the 24 months of the project to give an estimate of the hours required from each to support the project. Steve Goodacre (165 hours, 5% for 24 months) is Chief Investigator, Richard Wilson (660 hours, 20% for 24 months) will oversee project management, Mike Campbell (66 hours, 2% for 24 months) will oversee statistical plans and analysis, Andrew Lee (66 hours, 2% for 24 months) will provide public health expertise, Ian Machonochie (33 hours, 1% for 24 months) will provide paediatric emergency medicine expertise, Andrew Bentley (33 hours, 1% for 24 months) will provide critical care expertise and Darren Walter (33 hours, 1% for 24 months) and Kirsty Challen (PhD student) will provide specific expertise in the assessment of suspected pandemic influenza.

During the pilot phase we will require two additional research associates (RA6, 100% for 6 months and 100% for 12 months), a clerical assistant (50% for 12 months) and the following Clinical Trials Unit support:
Database set up and maintenance £5775
Data entry and management £6853

During the pandemic phase we will require two additional research associates (RA6, 100% for 6 months and 100% for 9 months), a statistician (RA7, 50% for 6 months) to undertake analysis, a clerical assistant (20% for 12 months) and the following Clinical Trials Unit support:
Database refinement and maintenance £3975
Data collection form production £546
Data entry 20,000 data collection forms and management £40950
Data management £7095

We are also requesting £5000 costs to cover project management and steering committee meeting travel and subsistence, conference fees, and to support the public and patient representative activities of members of the Sheffield Emergency Care Forum; and £3000 for computing equipment (one laptop @ £750 for each of four researchers).

The NHS support costs will fund CLRN research nurses in each hospital to photocopy the form, check data accuracy, check computer records at 30 days and review case notes of 15% who have re-attended the hospital. We have estimated a higher cost per patient in the pilot phase to allow for developing and refining processes, and will use the pilot study to obtain an accurate estimate of anticipated NHS costs for the main study.

For the pilot study we have assumed that 30 minutes per patient of band 6 research nurse time (£35 per hour) will be required for photocopying, data checks and computer record review, plus a further 30 minutes for the 15% who require case note review. Thus 400 cases @ £20 per patient = £8000.

For the main study we have assumed that only 10 minutes per patient will be required for photocopying, data checks and computer record review, but 30 minutes is still needed for the 15% who require case note review. Thus 20,000 cases @ £9 per patient = £180,000.

The University of Sheffield has joined phase 3 of the Carbon Trust’s Higher Education Carbon Management Programme. This programme is designed to deliver improved energy management of academic, accommodation and leisure buildings and vehicle fleets. It also provides practical support to organisations by helping them identify carbon saving opportunities, providing software to analyse energy consumption and delivering workshop support for staff and senior managers to improve their awareness of energy efficiency.

Our proposal will seek to minimise greenhouse gas emissions in the following ways:
1. Conducting project management meetings by teleconference where possible
2. Conducting meetings in a central location that is accessible by public transport
3. Disseminating findings using electronic media where possible
4. Using public transport to travel to conferences
References:

Flow diagram

1. **Patient attends Emergency Department**
   - **Meets clinical diagnostic criteria for suspected pandemic influenza?**
     - **No** → **Not eligible**
     - **Yes**

2. **Medical staff complete data collection form**
   - **Copy secured in emergency department notes**
   - **Copy taken by CLRn nurse**

3. **Patient managed as normal, according to medical decision and DH guidance**

4. **Self-discharge or transfer**
   - **GP contact**

5. **Admitted**
   - **CLRn nurse tracks progress up to outcome or 30 days**

6. **Discharged**
   - **CLRn nurse reviews computer records, and notes if any subsequent admission, at 30 days**
### Appendix: Studies evaluating clinical predictors of adverse outcome in pandemic influenza

<table>
<thead>
<tr>
<th>Author</th>
<th>Site</th>
<th>Subjects</th>
<th>N</th>
<th>Outcome</th>
<th>Variable</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rowan (ICNARC) [10]</td>
<td>UK</td>
<td>ICU suspected H1N1 (nb only 562 confirmed)</td>
<td>1725</td>
<td>Death</td>
<td>Current/recent pregnancy, Severe chronic organ dysfunction, Immunocompromise, SOFA score (per point)</td>
<td>HR 0.13 (0.19-0.98) p=0.048 HR 1.53 (1.16-2.02) p=0.008 HR 1.65 (1.16-2.33) p=0.005 HR 1.05 (1.02-1.08) p=0.001</td>
</tr>
<tr>
<td>Miller [13]</td>
<td>Utah</td>
<td>ICU adm age&gt;15 PCR confirmation H1N1</td>
<td>47</td>
<td>ICU admission</td>
<td>Hispanic, Pacific/Hawaiian, BMI 30-39, BMI &gt;39</td>
<td>23% v 13% popn p=0.01 26% v 1% popn p&lt;0.001 38% v 19% popn p&lt;0.001 36% v 3% popn p=0.001</td>
</tr>
<tr>
<td>Nguyen-van-Tam (fluCIN) [14]</td>
<td>UK</td>
<td>Hospitalised confirmed H1N1</td>
<td>631</td>
<td>Death/ICU/HDU</td>
<td>Chronic lung dis (not asthma/COPD)* Obesity* Altered consciousness CXR pneumonia* CRP &gt;100* SaO2&lt;94% on air</td>
<td>OR 3.41 (1.33-8.71) p=0.010 OR 6.96 (1.46-27.28) p=0.008 OR 1.11 (1.04-1.17) p=0.001 OR 5.28 (2.95-9.47) p=0.001 OR 4.41 (2.14-9.1) p=0.001 OR 3.6 (2.17-6.27) p=0.001</td>
</tr>
<tr>
<td>ANZIC [15]</td>
<td>Australia/NZ</td>
<td>ICU confirmed H1N1</td>
<td>722</td>
<td>ICU admission</td>
<td>Pregnancy, BMI &gt;35, Chronic pulm disease, Maori/Pacific islands</td>
<td>9.1% v 1% popn 28.6% v 5.3% popn 32.7% v 13% popn 25% v 13.6% popn</td>
</tr>
<tr>
<td>Harris [16]</td>
<td>Australia</td>
<td>H1N1 confirmed</td>
<td>181</td>
<td>Hosp admission</td>
<td>Aboriginal/Torres Strait Pregnant, Diabetes, Renal disease, Cardiac disease, Obese</td>
<td>37.7% v 60.3% p=0.004 29% v 8.1% p=0.013 24.6% v 4.2% p&lt;0.001 18% v 3.3% p&lt;0.001 26.2% v 8.3% p=0.001 28.3% v 10% p=0.002</td>
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<tr>
<td>Santaolalla [17]</td>
<td>Spain</td>
<td>Inpatients H1N1</td>
<td>3025</td>
<td>ICU/death</td>
<td>Asthma, COPD, BMI &gt;40, Diabetes, Other metabolic disease, Cardiovascular disease, Chronic hepatic disease, Seizures, Chronic renal insufficiency</td>
<td>14.5% v 22.7% p&lt;0.001 11.5% v 16.9% p&lt;0.001 19.3% v 11.1% p&lt;0.001 13.8% v 9.4% p&lt;0.001 11.5% v 8.8% p=0.001 16.1% v 9.6% p&lt;0.001 9% v 6.1% p=0.025 6.5% v 3.4% p=0.001 7.3% v 4.1% p=0.003</td>
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<tr>
<td>Cui [18]</td>
<td>China</td>
<td>Inpatient H1N1</td>
<td>68</td>
<td>Death</td>
<td>BMI &gt;27</td>
<td>8/10 death v 1/43 alive p=0.001</td>
</tr>
<tr>
<td>Zimmerman [19]</td>
<td>Tel Aviv</td>
<td>Adults, CDC definition, PCR confirmation</td>
<td>191</td>
<td>ICU admission</td>
<td>SaO2, Exam lung findings, CRP</td>
<td>Median 92% v 97% p=0.006 71% v 31% p=0.002 Median 123 v 40 p&lt;0.001</td>
</tr>
<tr>
<td>Martin-Loeches [20]</td>
<td>Spain</td>
<td>Adults, ICU admission for respiratory failure, no pre-existing CRF, microbiological confirmation</td>
<td>661</td>
<td>Acute kidney injury</td>
<td>Diabetes, SOFA score, MODS, WCC, CK, CRP</td>
<td>16.2% v 9.2% p=0.04 Mean 8.7 v 4.8 p&lt;0.001 92.4% v 54.7% p&lt;0.001 8.3 v 6.8 p&lt;0.001 290 v 170 p&lt;0.001 28 v 20 p&lt;0.001</td>
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<tr>
<td>Louie [22]</td>
<td>US</td>
<td>Age&lt;18 hospitalised H1N1</td>
<td>345</td>
<td>Death/ICU</td>
<td>Hispanic (v white), Pulmonary disease, Cardiac disease, Neuro disease</td>
<td>OR 0.4 (0.2-0.8) OR 1.6 (1.0-2.6) OR 4.3 (1.9-9.5) OR 2.8 (1.6-5.0)</td>
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<tr>
<td>Study</td>
<td>Country</td>
<td>Region</td>
<td>Criteria</td>
<td>N</td>
<td>Setting</td>
<td>Event</td>
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<tr>
<td>Stein [23]</td>
<td>Israel</td>
<td>Age&lt;18 hospitalised H1N1</td>
<td>ICU admission</td>
<td>478</td>
<td>Neurologic disease</td>
<td>19% v 7.6% p&lt;0.02</td>
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<td>Vasoo [24]</td>
<td>USA</td>
<td>ED presentations H1N1</td>
<td>Admission</td>
<td>83</td>
<td>History of prematurity</td>
<td>18.8% v 0 p=0.002</td>
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<tr>
<td>Bagdure [25]</td>
<td>USA</td>
<td>Paediatric adm H1N1</td>
<td>PICU</td>
<td>307</td>
<td>Neurologic disorder</td>
<td>38% v 19% p=0.002</td>
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<tr>
<td>Fajardo-Dolci [27]</td>
<td>Mexico</td>
<td>First 100 H1N1 confirmed deaths</td>
<td>Death</td>
<td>100</td>
<td>Cardiovascular disease</td>
<td>20.9% v 4.1% popn</td>
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<tr>
<td>Lee [28]</td>
<td>Hong Kong</td>
<td>Adults seasonal flu A/B</td>
<td>Death</td>
<td>754</td>
<td>Oseltamivir</td>
<td>HR 0.27 (0.13-0.55) p&lt;0.001</td>
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<tr>
<td>Libster [29]</td>
<td>Argentina</td>
<td>Age &lt;18 confirmed H1N1 by PCR</td>
<td>ICU admission</td>
<td>251</td>
<td>Asthma</td>
<td>OR 4.92 (1.38-17.33) p=0.002</td>
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<td>Chien [30]</td>
<td>Korea</td>
<td>H1N1 pneumonia</td>
<td>IPPV/NIV</td>
<td>96</td>
<td>Pregnancy</td>
<td>2% v 9% p=0.05</td>
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<td>Jain [31]</td>
<td>US</td>
<td>Confirmed H1N1</td>
<td>ICU/death</td>
<td>272</td>
<td>Age Neurocognitive disease</td>
<td>Median 19 v 29</td>
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<td>Tuite [32]</td>
<td>Canada</td>
<td>Confirmed H1N1</td>
<td>Death</td>
<td>3152</td>
<td>Age &gt;50</td>
<td>OR 28.6 (7.3-111.2)</td>
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<td>Campbell [33]</td>
<td>Canada</td>
<td>Hospital admission H1N1</td>
<td>Death/ICU</td>
<td>1479</td>
<td>Heart disease Diabetes</td>
<td>RR 2.1 (1.6-2.7)</td>
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<td>Authors</td>
<td>Country</td>
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<td>N</td>
<td>Outcomes</td>
<td>RR (95% CI)</td>
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<td>Aviram</td>
<td>Israel</td>
<td>ED H1N1 CXR in 24h</td>
<td>97</td>
<td>ICU/death Bilateral</td>
<td>1.5 (1.1-2.0)</td>
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<td>opacities Multizonal</td>
<td>60% vs 15% p=0.049</td>
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<td>60% vs 6% p=0.01</td>
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<td>Bassetti</td>
<td>Italy</td>
<td>Inpatients confirmed H1N1</td>
<td>81</td>
<td>ICU/death Neurocognitive</td>
<td>33.3% vs 7% p=0.02</td>
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<td>disease COPD/asthma</td>
<td>19.7% vs 50% p=0.03</td>
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<td>Pneumonia on admission</td>
<td>100% vs 44% p=0.0008</td>
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<td>Xi</td>
<td>China</td>
<td>Adult inpatients H1N1</td>
<td>155</td>
<td>Inpatient death Hypertension</td>
<td>37% vs 19.5% p=0.048</td>
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<td>Dyspnoea at presentation</td>
<td>77.8% vs 47.7% p=0.004</td>
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<td>Pebody</td>
<td>UK</td>
<td>UK national statistics (estimated case fatality rate)</td>
<td>440</td>
<td>Death Chronic renal</td>
<td>RR 36.3 (20.9-63.2)</td>
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<td>disease Heart disease</td>
<td>RR 15.2 (9.6-24.1)</td>
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<td>Respiratory disease Liver</td>
<td>RR 11.3 (7.9-16.1)</td>
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<td>disease Diabetes Immunosuppression</td>
<td>RR 63.3 (38.6-103.7)</td>
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<td>Stroke/TIA Chronic</td>
<td>RR 9.2 (5.6-14.9)</td>
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<td>neurological disease</td>
<td>RR 52.8 (36.3-76.6)</td>
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<td>disease</td>
<td>RR 7.5 (2.3-23.7)</td>
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<td>RR 115.3 (84.3-157.6)</td>
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<td>Wilking</td>
<td>Germany</td>
<td>National statistics</td>
<td>22607</td>
<td>Death Age 15-34 (ref 35-60)</td>
<td>OR 0.18 (0.13-0.26)</td>
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<td>5</td>
<td>Age &gt;60</td>
<td>OR 5.4 (3.86-7.56)</td>
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</table>