Long Title: Real time refinement and validation of criteria and tools used in primary care to aid hospital referral decisions for patients of all ages in the event of surge during an influenza pandemic.

Short Title: Evaluation and refinement of pandemic influenza community assessment tools (the FLU-CATs study)

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SUMMARY

Design: A prospective analysis, linking criteria in a GP's assessment of patients presenting with syndromic acute respiratory disease (such as influenza like illness or COVID-19), to immediate management decisions and patient outcomes.

Objective: Assessment, refinement and validation of various triage tools to guide GP referral of patients with syndromic acute respiratory disease (such as influenza like illness or COVID-19) during a pandemic in readiness for use should widespread illness exceed health care capacity (surge).

Method: GPs using electronic Health Records (eHRs) will record their assessment and management of patients with syndromic respiratory disease (such as influenza like illness or COVID-19) which includes COVID-19, in the routine electronic health care systems. These assessments may be made face-to-face or remotely by telephone or video. The eHRs automatically offer structured data capture as templates for various clinical presentations. Such a template has been prepared for use in the event of an outbreak of **any pathogen of public health interest,** initially with intent to function for syndromic presentation of a respiratory illness caused by a novel respiratory viral threat such as a novel influenza or coronavirus.

High level hospital discharge data are routinely uploaded from secondary care to the eHRs including hospital admission date, discharge date, main disease code, main procedure code, discharge date or date of death in hospital. Death in the 30 days following consultation will also be captured.

The providers of the eHRs EMISWeb / SystmOne will provide the relevant data extract to the investigators researchers on a weekly basis.

Where available, a further analysis will be performed against those cases with a proven diagnosis based on point of care tests (finger prick, swabs) and any diagnostic information that is available at or shortly after the consultation.

Analysis: Automated weekly cumulative and rolling interval analyses are planned.

Univariate and multivariate analyses using unconditional logistic regression will be used to investigate the association between proposed triage criteria threshold values and primary outcomes (hospital admission, and death) and secondary outcomes (length of stay and augmented levels of care (high dependency / intensive care)). The threshold values of triage criteria will be refined by comparing the receiver operator characteristics at various thresholds of abnormality (e.g. respiratory rate >30, >35, >40).

The discriminatory value of existing and refined triage tools will be compared using logistic regression. Triage tools will be compared for their ability to predict outcomes using Area Under the Receiver Operating Characteristic Curve (AUROC) comparisons. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) will be calculated for triage tools using different score thresholds.

The virus, human behaviour, and models of health care provision in the community may change in time. Analysis will be reset between pandemic waves and appropriate comparisons made between pandemic waves.

TIMELINE

Phase one: (inter-pandemic – development / feasibility testing), duration six months during a summer season: set-up and validation of processes; optimisation of the clinical record entry screen (consultation template); GP acceptability testing; establish data-return format; check completeness of data returns; develop data clean-up algorithms; development of definitions, evaluation of completeness and validation of study outcomes using historical GPRD and HES data; test of LEPIS study link. This will involve 3 to 5 practices experienced in developing GPRD/LEPIS research protocols.

Phase two: (inter-pandemic – pilot), duration six months in the consecutive winter season in 50 practices. Using data from cases of influenza like illness: test data-cleaning algorithms and the automated weekly evaluation of performance of triage criteria and tools. Rehearse report preparation to match expected "battle rhythm" of key pandemic policy advisory bodies (SAGE & PICO). The project will be mothballed at end of phase two.

Phase three: will be activated in the event of a pandemic. The study data query set in included within a general COVID-19 consultation template that has been provided by the two major electronic Health Record providers across their estate in a routine update. EMIS serves ~4200 practices (56%), SystmOne ~2552 (34%), VisionHealth ~636 (9%) and Microtest ~1% practices in England. The template has been shared with the two minority eHR providers VisionHealth and Microtest, though at present they are not involved in the study. Background processes will offer the COVID-19 template to GPs to document consultations (face-to-face or remote) for presenting with influenza like illness such as COVID-19. The eHR providers will provide weekly data returns to the investigators, who will run automated cumulative and rolling interval analysis against primary outcomes. This will allow rapid refinement of criteria and tools for use against the novel pandemic virus, and plan adaptation of tools in readiness of surge.

An outline of the study as it would run in phases two and three is presented on page 19 (figure 3).

INTRODUCTION

The potential for health care demand to exceed clinical capacity (surge) is recognised in historic reports of influenza pandemics and current government guidance.[1,2] Clinical triage tools capable of identifying the need for higher levels of care and risk of severe outcome have an important role in pandemic situations where secondary care capacity may be insufficient to meet demand; the time available for clinical decision making may be limited by workload pressures; and healthcare workers unfamiliar with clinical assessment and admission decision making may be asked to fulfil 'gatekeeper' roles.[3]

CURB-65 is a validated predictor of mortality from community acquired pneumonia in adults but was never intended for use in children.[4,5] CURB-65 does not perform as well in predicting higher levels of care and was not designed to predict mortality from non-pneumonic presentations.[6,7] Challen et al proposed the Pandemic Medical Early Warning Score (PMEWS) as a clinical triage tool to aid hospital admission decisions for adults in a pandemic situation.[8] They validated PMEWS in adults presenting to hospital with community acquired pneumonia and found that it was better than CURB-65 for predicting the need for admission and higher levels of care but had limited ability to predict mortality. CURB-65 and PMEWS pose problems for use in primary care, the first being in-part reliant upon a contemporaneous serum urea value and the second is computationally complicated. Other severity scoring tools exist, but these are not suitable for use in primary care due to a greater dependence upon laboratory or radiological investigations.

In 2009, the Department of Health England published a package of care that included Paediatric and Adult Community Assessment Tools (CATs) and patient pathways for use by the NHS in a severe pandemic event.[9] CATS were developed to help non-specialist front-line staff identify which sick children and adults are most likely to benefit from interventions and levels of care only available in hospitals when resources are limited. CATs were developed by paediatric and adult expert clinical development groups drawing on evidence that supports the recognition of severe influenza and severe pneumonia in the community in adults and children in resource limited settings; severe chronic obstructive pulmonary disease in adults; potentially serious feverish illness in children; and severe bronchiolitis in infants.[3,10,11,12,13,14,15,16,17,18,19] Clinicians were warned not to use the CATs and the pathways unless the local situation precluded normal admission and discharge processes.

CATs use six objective and one subjective criterion based on simple clinical assessment (figure 1). Meeting any CAT criterion warrants referral and admission to hospital. Criteria are: A) severe respiratory distress, B) increased respiratory rate, C) oxygen saturation ≤ 92% on pulse oximetry breathing air or oxygen, D) respiratory exhaustion, E) severe dehydration or shock, F) altered consciousness level and G) other clinical concern. While criteria fields are common to adult and paediatric CATs, the abnormal physiological thresholds and clinical signs are age appropriate. Like PMEWS, there is no requirement for laboratory investigation to complete the assessment. However CATs were only intended for use "during severe and exceptional circumstances when surge demand for healthcare services leads to a need for strict triage"; and as such, were not deployed during the 2009/10 pandemic.

Work underpinning this study.

Goodacre and colleagues (2010) conducted an evaluation of the discriminatory value of the CURB-65 score, PMEWS and CATs for predicting severe illness or mortality in patients with suspected pandemic influenza, but were unable to draw any conclusions regarding their clinical utility in a pandemic situation due to insufficient case numbers especially of adults, and a low incidence of severe outcome.[20]

Semple, Myles, Van-Tam and other members of the UK Pandemic Influenza Clinical Information Network (FLU-CIN) characterised PCR-confirmed pandemic influenza disease in a much larger cohort of 1520 people (1040 adults, 480 children (age <16 years)) admitted to hospital.[21] (Thorax submitted) FLU-CIN compared the clinical validity and utility of CATs, PMEWS and CURB-65 as predictors for interventions normally only available in hospital, higher levels of care, and death using area under the Receiver Operating Characteristic (ROC) curve (AUROC) comparisons with 95% confidence intervals (paper submitted).[22] CATs showed the best predictive performance for level 2/3 admissions in both adults [AUROC: CAT 0.77 (0.73, 0.80); CURB-65 0.68 (0.64, 0.72); PMEWS 0.68 (0.64, 0.73), comparison of AUROCs $p<0.001$] and children [AUROC: CAT 0.74 (0.68, 0.80); CURB-65 0.52 (0.46, 0.59); PMEWS 0.69 (0.62, 0.75), $p<0.001$].

While the FLU-CIN cohort is limited to patients admitted to hospital with severe influenza and its complications, the data show that triage tools are capable of predicting higher levels or care and or death in children and adults. However the FLU-CIN analysis does not include assessment of triage tools in primary care.

Appropriate use of such triage tools in the community could expedite referral to hospital and where scores are high, immediate admission to level 2/3 care. Prompt admission and allocation of higher levels of care may be associated with improved patient outcomes. Another study by FLU-CIN found that delayed admission to hospital (≥4 days after symptom onset) was significantly associated with increased likelihood of admission to critical care and death.[23]

The validity and utility of using triage tools in the community remains untested. Morbidity and mortality rates were low during the H1N1(2009) event when compared to some previous influenza epidemics such as the one in 1989/90 [24] and the use of anti-viral therapy was generally low in the FLU-CIN cohort despite it being widely available at the time. A more severe pandemic may be associated with a greater acceptance of anti-viral therapy and this may impact upon need for higher levels of care and death. Consequently criteria threshold values may need to be adjusted to optimize the ROC for each criterion and the AUROCs for the various triage tools. Despite the adaptation of the National Pandemic Influenza Service algorithm for COVID-19 and provision of this service by the NHS 111 telephone number, GPs are still frequently assessing people with syndromic acute respiratory infection in the community. Patients present through usual channels, require assessment in long-term care facilities and at community “Hot Clinics”.

Justification of this study

The validity and utility of the various triage tools needs to be assessed in a large community-based prospective study of patients consulting with GPs with syndrome acute respiratory infection such as influenza like illness and COVID-19. This is needed to give confidence to GPs who may be asked to use such tools in the event of surge, and policy makers who may need to recommend their use to GPs.

It would not be possible to conduct this study during a pandemic without prior development of processes, feasibility and pilot studies.

The Health Protection Agency timeline for the UK 2009 pandemic shows only 12 weeks between identification of person-to-person transmission in the UK (first week May) and peak influenza activity (last week July) in the first pandemic wave. Prospective data collection with near real-time iterative and cumulative analysis is the only method for validating triage criteria and tools against a novel pathogen in such a short time.

Since pandemics are unpredictable and infrequent, limited but potentially useful information will be gained from prospective feasibility and pilot work conducted in primary care during seasonal influenza while H1N1v is still circulating.

Conducting this study in real-time during the early stages of a pandemic, when the characteristics of the novel virus are not fully understood, is important as it allows refinement and validation of triage tools against the novel pathogen in preparation for possible surge. This cannot be done until a novel virus emerges. Dame Diedre Hine has recommended that population based studies be established that, in the early stages of a future pandemic, can measure the severity of the pandemic and support decision making.[25]

The study method adheres to the five principles of Dynamic Risk Assessment and as applied to the management of emergency situations by UK Government agencies (Evaluate, Select, Assess, Refine, Reassess) (Home Office Guide to Operational Risk Assessment - Generic Risk Assessment 3.2. (Version 2 September 2008)).

If, as in the 1918/19 epidemic the behaviour of the virus is markedly different in terms of severity between the first and subsequent waves or evolves to cause severe disease in a particular organ system; then triage criteria may need to be adapted to reflect the consequent changes in health care demand and clinical presentation.

RESEARCH OBJECTIVES

Aim

To establish processes now, that can be used in the early stages of a future pandemic event to provide valid community triage tools capable of assisting hospital referral decisions for people of all ages for use if health care demands exceed health care capacity (surge).

Primary objective

From the start of a future pandemic event, to describe on a weekly cumulative basis the association between various triage tools and pandemic influenza outcomes. This will be supplemented as appropriate, with receiver operator characteristic (ROC) curves analysis and predictive values (positive and negative) of various community triage tools (Adult and Paediatric CATs, PMEWS) to predict outcomes (hospital admission and or death) in people of all ages presenting with pandemic influenza like illness to a large number of general practices in the UK; and to feed this information back to policy makers via the New Emerging Respiratory Virus Threat Advisory Group (NERVTAG), COVID-19 Clinical Information Network (CO-CIN) and members of the Scientific Advisory Group for Emergencies (SAGE).

Secondary objectives

1. To provide reassurance that it is safe for people who do not meet triage criteria and so would not be referred for hospital admission to continue to be managed in the community with self-care advice.
2. To describe the associations between specific triage criteria and outcomes (hospital admission, length of stay, need for higher levels of care and or death).

3. Using sensitivity analysis to refine threshold values for specific triage criteria and outcomes (hospital admission, length of stay, need for higher levels of care and or death).
4. To describe demographics and clinical features of patients that meet threshold criteria and are referred for admission by GPs but are declined admission on assessment at hospital.
5. To describe demographics and clinical features of patients that present with syndromic acute respiratory infections such as influenza like illness or COVID-19 to GPs and after assessment are not considered to need referral to hospital yet die in the community within 30 days.
6. To describe demographics and clinical features of patients that present with influenza like illness to GPs and after assessment are not considered to need referral to hospital yet die in hospital within 30 days.

We will analyse,

1. Separately by age group: adults and children (<16 years)
2. Cumulatively for primary objectives.
3. Weekly for primary objectives from initiation of study.
4. Three monthly for secondary objectives

Policy related

To provide evidence and reassurance to clinicians, policy makers and Ministers that any triage tools recommend for use in the event of surge are validated against the novel pathogen, are safe to use and clinically justified.

PLAN OF STUDY

The study will run in three phases:

- **Phase one** (inter-pandemic - development & feasibility). Proposed start date 01.04.2012. Duration six months during a summer season.

  At the start of this project, the researchers will evaluate in detail the validity and completeness of recording of the outcome measures in GPRD (analysing the data as collected up to the start of the study). Code lists will be developed. The frequency of recording of various data fields will be evaluated. In addition, comparisons will be made with HES in order to assess the completeness of recording of hospital admissions. These analyses will provide important information about the quality of GP recording of the outcomes. Based on the large number of published validation studies with GPRD, it is expected that major clinical outcomes are generally recorded well by GPs but that clinical details (such as length of hospital stay) may be less complete.

  We will set-up and test the technology processes. This will involve 3 to 5 GP practices experienced in developing GPRD research protocols GPs will be involved in optimising the study record entry screen in LEPIS and do user acceptability testing. We will establish the data-return formats; check completeness of data recording by GPs in LEPIS; develop data clean-up algorithms; development of definitions, evaluation of completeness and validation of study outcomes using historical GPRD and HES data; test LEPIS study link.

  There will be meetings with the oversight committee prior to commencement, at mid point and end of phase one.

- **Phase two** (inter-pandemic – pilot), Proposed start date 01.10.2012. Duration six months in the consecutive winter season in 50 practices. Using data from cases of influenza like illness: test data-cleaning algorithms and the automated weekly evaluation of performance of triage criteria and tools. We will rehearse report preparation to match expected “battle rhythm” of key pandemic advisory bodies (SAGE & PICO). There will be meetings with the oversight committee prior to commencement, at mid point and end of phase two. The project will be mothballed at end of phase two.

- **Phase three** will be activated in the event of a pandemic. The study data queries are included within a general COVID-19 consultation template that has been provided by the two major electronic Health Record providers across their estate in a routine update. EMIS serves ~4200 practices (56%), SystmOne ~2552 (34%), VisionHealth ~636 (9%) and Microtest ~1% practices in England. The template has been shared with the two minority eHR providers VisionHealth and Microtest, though at present they are not involved in the study. Background processes will offer the COVID-19 template to GPs to document consultations (face-to-face or remote) for presenting with influenza like illness such as COVID-19. We will run a weekly cumulative analysis against outcomes, allowing frequent refinement of criteria and tools against the novel pandemic strain, and plan adaptation for use in readiness of surge.

In the event of imminent surge, and at the direction of policy makers at devolved Departments of Health, it will be possible to provide an algorithm behind the clinical record page in eHR that will indicate that triage criteria have been met and so prompt the GP to consider hospital referral. Regional variations of eHR software are provided to practices in devolved UK administrations, which will allow for variations in regional policy. A decision by one administration not to offer triage tools during surge would be respected by not deploying the algorithm in that region. The study will continue during surge. The indication that triage criteria have been met could be removed when surge has ceased while the study will continue.

EXISTING RESEARCH

There have been two head to head comparisons of the triage tools proposed by DH guidance, both in cohort of patients already admitted to hospital.[20,22]

The validity and utility of using PMEWs, CATs (both triage tools) and CURB-65 (a validated predictor of mortality from community aquired pneumonia) to predict augmented levels of care and or death has been studied by the FLU-CIN in 1520 patients *admitted to hospital* with confirmed pandemic influenza A(H1N1)2009[22].

The ROC curves and AUROC values comparing the predictive value of the three clinical triage tools are described in figure 2. CATs showed the best predictive performance for augmented higher levels of care (effectively HDU & ITU admissions) in both adults [AUROC: CAT 0.77 (0.73, 0.80); CURB-65 0.68 (0.64, 0.72); PMEWS 0.68 (0.64, 0.73), comparison of AUROCs $p<0.001$] and children [AUROC: CAT 0.74 (0.68, 0.80); CURB-65 0.52 (0.46, 0.59); PMEWS 0.69 (0.62, 0.75), $p<0.001$]. CURB-65 and CAT had similar performance in predicting mortality in adults [AUROC: CAT 0.70 (0.63, 0.77); CURB-65 0.71 (0.65, 0.77); PME 5WS 0.60 (0.52, 0.67), $p=0.009$] but CAT performed best as a predictor of mortality in children [AUROC: CAT 0.76 (0.66, 0.86); CURB-65 0.51 (0.39, 0.63); PMEWS 0.69 (0.55, 0.83), $p=0.002$].

The receiver operator characteristic, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for each of the tools using various score thresholds (table 1). In adults, a CAT score ≥3 was the best predictor of level 2/3 admissions, death and combined severe outcome when compared to various cut-off scores for either CURB-65 or PMEWS. In children, a CAT score ≥3 was the best predictor of level 2/3 admission and combined severe outcome; performing marginally better than a PMEWS score >9, both significantly better than CURB-65. In children, a PMEWS score >9 was the best predictor of mortality in children; performing marginally better than a CAT score >3, both significantly better than CURB-65.

Anonymised electronic general practice data has been used extensively across a wide spectrum of disease areas including seasonal and pandemic influenza. Watkins et al used GPRD to determine the burden of seasonal influenza in childhood.[26] Hansell et al (1999) investigated the epidemiology of respiratory disorders adopting similar methods.[27] Mangtani et al (2004) investigated the effectiveness of influenza vaccination in the elderly.[28] Time series analysis of a similar nature to this proposed study was undertaken by Hajat et al (1999) to determine the relationship between pollution and consultations for asthma and lower respiratory disorders.[29] [30]

RESEARCH METHODS

Study design – prospective observational maximum capture study using anonymised usual electronic health record data linked to extended hospital episode summary data with near real-time dynamic analysis

It is important to note that there will be no specific interventions made by the study.

None of the clinical features that constitute triage criteria are novel.

All clinical feature of interest are examined albeit with variations of adherence in current community practise.

Recruitment Population

Any person presenting to a general practice or other community care setting (walk-in-centre or hot clinic) for consultation (whether direct or remote) with a General Practitioner or Primary Care Nurse Practitioner regardless of date of onset of disease and prior medical history.

GPs are recognised to be committed to improving the health of their communities by providing anonymised data for a number of research and quality of service audit purposes.

Structured data collection templates with reminder processes are now in routine use for context specific consultations, with background processes that allow data extraction for regularly uploaded to LEPIS and linked to Vision® in-practice software for research and quality of service audit purposes.

Inclusion criteria

Any person presenting to a general practice or other community care setting (walk-in-centre or hot clinic) with syndromic acute respiratory infections such as influenza like illness or COVID-19 regardless of date of onset of disease and prior medical history.

Exclusion criteria

People who present with any condition other than syndromic acute respiratory infections such as influenza like illness or COVID-19.

Proposed sample size

A formal sample size calculation is not possible and will depend to a great extent upon the clinical attack rate and hospitalisation rate (severity) of the pandemic strain. The clinical attack rate and hospitalisation rate of a future pandemic strain cannot be guessed, however the recent “mild” pandemic does provide useful information.

In the first wave of the 2009 pandemic the clinical attack rate varied considerably between regions from 446 cases per 100,000 in the rural South-West to 1344 cases per 100,000 in London.[31] Most people experienced a mild, typical influenza-like illness and the overall rate of hospitalisation ranged from 1.3% to 2.5% of those affected.

Based on the limits of the clinical attack rates during the 2009 event; between 23,000 and 69,000 of these people would be expected to present in the first wave. Approximately 10,000 to 30,000 of these patients will present in the first 3 months before peak activity; forming the study cohort available for assessing, refining and validating triage tools in preparation for surge. Based on the limits of the hospitalisation rates previous described, 130 to 750 of these people would be admitted to hospital forming the group with a positive primary outcome measure in this study.

The FLU-CIN study was able to validate triage tools using similar method of analyses in a cohort of 1520 patients admitted to hospital where the positive primary outcomes groups comprised 250 (16.5%) people who required higher levels of care (level 2 HDU or 3 - ITU) and 80 (5.3%) who died.

During a pandemic event, and subject to timely activation of the study, the provision of data from an outbreak specific consultation template across the primary care estate is expected to provide data from more than 1500 assessments in England.

Thus we are confident that this study will be sufficiently powered to assess, refine and validate the triage tools in the timetable described.

Data Sources:

The General Practise Research Database (GPRD) and linked Hospital Episode data

The GPRD research group were named co-investigators in this application for phase 1 and 2 of the study but have left the collaboration.

The General Practice Research Database (GPRD) is the world's largest database of anonymised longitudinal medical records from primary care. The Secretary of State for Heath has owned the database since 1994. The GPRD is managed by Medicines and Healthcare products Regulatory Agency (MHRA). The database comprises near real-time comprehensive observational data from over 1000 GPs working in 629 general practices. It is a valuable tool for academic research in a broad range of areas including clinical epidemiology, disease patterns, disease management, outcomes research, and drug utilisation. The quality and reputation of the GPRD data make it an invaluable resource for researchers. There have been over 890 research papers published in peer-reviewed journals using data from this database. In July 2011 data was being collected on 5.14 million active patients of research standard or 8.3% of the UK population attending. The GPRD closely reflects the age, gender, and geographic distribution of the UK.[32] The quality of GPRD data has recently been reported in a systematic review. [33] While some acute musculoskeletal and metabolic conditions are not well recorded in GPRD, the majority of diagnoses were reliably coded and there is good agreement between more

common diseases and other datasets. Importantly fro this study, influenza incidence rates derived from GPRD agree closely with data from national influenza surveillance systems.[30]

Detailed Hospital Episode Summary (HES) data is linked to GPRD every three months. HES data includes: detailed disease codes (ICD-10), procedure codes, levels of augmented care, length of stay and death. The ability of GPRD to conduct research across linked databases using this detailed clinical record data has been proven in a population-based study on incidence, risk factors, clinical complications and drug utilisation associated with seasonal influenza.[34]

GP clinical assessments and immediate management decisions are recorded on GPRD/LEPIS at time of consultation. This data is downloaded nightly and collated for access by researchers on a weekly basis. Data on hospital admission and death is typically entered on GPRD with in 48 hours of receipt of notification. Recently Jick et al (2011) described the ability of GPRD to provide near real-time analysis of the epidemiology of pandemic influenza 2009.[35]

GPRD research group has gained ethical and National Information Governance Board (NIGB) approval to provide anonymised data and other healthcare data linked via the patient's NHS number, sex, date of birth and post code.

GPs who contribute to the database use Vision® (In Practice Systems Ltd); a computer software package designed by an established user-group of experienced GPs, to make contemporaneous records of their routine consultations and enter study specific data in LEPIS; a linked application maintained by the GPRD research team.

General Practitioners participating in the GPRD will be prompted on screen to record their assessment and management of patients presenting with influenza like illness. A flag will appear during consultation requesting the GP to complete their assessment on the LEPIS study website. This is the limit of any variation from routine practise; which is to record assessment and key positive and negative rule-out features in in free text fields in Vision®. It is important to note that GP are not expected to diverge from their routine clinical assessment of patients and that GP management decisions are already routinely entered in Vision®.

Hospitals are required to transmit discharge summaries to GPs within 48 hours or suffer financial penalties. These contain high-level data: primary diagnosis, date of admission, date of discharge or death. This data is manually input to Vision®, usually within 48 of receipt.

Linked anonymised Vision® and LEPIS data is downloaded nightly in a silent background application to the GPRD research group. Weekly extracts of the data are provided to the wider research community as the GPRD.

Linkage to Hospital Episode Summary (HES) data is done by an external NHS group in a way that the GPRD research team does not see any identifying details. HES data includes: method of admission, disease coding (ICD-10), length of stay, level of augmented care, procedural coding (OPCS classification of interventions and procedures, v4.6), cause of death as certified, prescribing and pharmaco-economics. Levels of augmented care are defined by the Department of Health and Intensive Care Society Standard (2009). These high-level data in HES have been mandated for return from all NHS hospitals in England for all patients admitted to since April 2006 to support payment by results. HES data is linked to GPRD at three monthly intervals and are provided to the wider research community.

The Office for National Statistics (ONS) collects information on causes of deaths from death certificates. ONS data is linked to HES monthly and to GPRD every three months.

Notification of death is made by hospitals to GPs via standard operating procedures that ensure this data is handled as a priority to prevent inappropriate communications and facilitate appropriate support to bereaved relatives. Thus death as a status is entered on Vision® with little delay. Notice of "hospital admission" is normally available within 48 hours of admission. The primary outcome measures of hospital admission and death are therefore available for use by GPRD following a nightly download. It is recognised that there is typically a delay of 48 hours after discharge before high-level hospital admission data is available from faxed hospital discharge letters. At the time of writing this proposal there is a 3-month interval in linkage of GPRD to HES and ONS certified cause of death data.

Part of our work in phases 1 and 2 will be study feasibility, conducting necessary validation and if necessary, initiate improved systems of data collection in the case of a pandemic.

Egton Medical Information Systems (EMIS) and SystmOne

EMIS serves approximately 4200 practices (56%) in England and uses a codex that allows harmonization with the other major eHR provider SystmOne. SystmOne serves approximately 2552 practices (34%) in England.

Applications were made to The Health Research Authority (HRA) and Confidentially Advisory Group (CAG) by IRAS to notify about an intended change in data provision for the study. The HRA Confidentiality Advisor stated on 13OCT2017, "I am unable to identify any additional breach of patient confidence outside that which is

covered by the Section 251 support already in place". The Health Research Authority in correspondence 23OCT2017 recognised the change of data provision from CPRD to EMIS and SystmOne. The changes were considered administrative non-substantive and are incorporated in this protocol.

Data management

All data analysis and will be maintained on secured computer servers within the University of Nottingham and University of Liverpool, only accessible to the research team and appropriately protected in accordance with Caldicott principles.

Definition of syndromic Influenza Like Illness and COVID-19

Influenza like illness (ILI) will be defined per the World Health Organisation criteria: "any person with sudden onset of fever (>38°C) and cough or sore throat in the absence of other diagnoses". This closely matches the Centres for Disease Control (CDC) USA definition used for community incidence studies: "fever or recent history of fever (≥37.8°C) plus cough and or sore throat in the absence of a known cause other than influenza". This definition will include those people meeting the British Infection Society/British Thoracic Society/Health Protection Agency/Department of Health (England) guidance criteria (2007): "presence or recent history of fever (T>38°C) plus new cough in the context of influenza circulating in the community". We have chosen not to adopt the Royal College of General Practitioners' Syndromic Surveillance System algorithm as it depends on self-reporting of muscle ache and or headache, which are poorly reported by young children.

It is accepted that the definition of ILI may be revised in the event of a future pandemic, either on the basis of on-going surveillance information or in the event of emergence of a novel pneumonic pathogen. This is not a concern. This study's aim is to establish automated processes capable of assessing and validating community triage tools in near-real time, which can be applied regardless of any variations of the case-defined entry criteria.

This definition will also identify COVID-19 cases.

Predictor variables

Clinical features of patients consulting for syndromic influenza like illness as recorded by GPs on eHRs during their routine consultation which include the criteria used by various triage tools:

1. Respiratory Rate (value)
2. Oxygen saturation (value)
3. Any sign of Severe Respiratory Distress (yes/no). Prompt "any of: lower chest wall indrawing, sternal recession, grunting, noisy breathing when calm, use of accessory muscles, supra-clavicular recession, tracheal tug, unable to complete sentences in one breath or feeling of suffocation.)
4. Respiratory Exhaustion (yes/no) or Apnoea reported (yes / no) -, apnoea defined as a ≥20 second pause in breathing
5. Blood pressure (systolic & diastolic values)
6. Sternal Capillary Refill Time (normal / >2secs)
7. Severe dehydration (yes/no). Prompt: "any of: reduced skin turgor, sunken eyes or fontanelle".
8. Adults only: New altered conscious level (Yes/ No). Prompt "any of: new confusion or disorientation in person, place or time; AVCPU score <A; or "Mini (abbreviated) mental test score <8".
9. Children only: New altered conscious level (Yes/ No). Prompt "any of: new confusion or disorientation in person, place or time; AVPU score < A; or Mini mental test score <8/10".
10. Strikingly agitated (yes / no)
11. New seizures (yes / no)
12. Floppy infant (yes / no)
13. Social isolation (yes / no). Prompt: "any of: lives alone; no fixed abode)
14. Chronic disease (yes / no). Prompt: "any of respiratory, cardiac, renal, metabolic, immune suppressed or sickle disease".
15. Causing other clinical concern to their GP (yes / no). Prompt with "For example a rapidly progressive or an unusually prolonged illness" (Yes / No)

Demographic data to be collected silently by background application

1. Practice location
2. Socioeconomic data at lower super output level (index of multiple deprivations)
3. Ethnicity
4. Sex
5. Age
6. In cases of death, Office of National Statistics cause of death

Outcome measures

Primary outcome measures

1. Hospital admission within 24 hours of GP assessment.
2. Death within 30 days of GP assessment (all causes). Complications leading to death may occur after some weeks (e.g. if prolonged admission to hospital). This outcome definition may miss cases that die as a direct consequence of their illness after 30 days, but based on 2009/10 experiences these are expected to be few.

Secondary outcome measures

1. Any need for augmented level of care during hospital admission i.e. level 2 – High Dependency and level 3 – Intensive/Critical Care, accepting that there are minor differences between paediatric and adult definitions of levels of care.
2. Length of hospital stay (stratified >48 hours, ≥6 days & ≥12 days)
3. GP's decision to refer for hospital admission.

Statistical analysis

Separate analyses will be made for paediatric and adult patients and will use age appropriate triage tools where available.

The datasets will be analysed using STATA statistical software.

Weekly cumulative analysis is planned using real-time data followed by 3-monthly validation using HES and ONS linked data. A rolling analysis is required because the virus, human behaviour, and models of health care provision in the community may change in time. The analyses will be reset in keeping with key policy changes in order to assess the impact of any changes. For example the introduction of that automated National Pandemic Flu Service (NPFS) in July 2009 substantially reduced the numbers and altered the case mix of people presenting to GPs.[31]

Univariate and multivariate analysis (using unconditional logistic regression) will be used to investigate the association between triage criteria threshold values and primary outcomes (hospital admission and or death). The threshold values of triage criteria will be refined by describing the receiver operator characteristics of different thresholds of abnormality (e.g. respiratory rate >30, >35, > 40) to predict patient outcomes.

It is likely that in the first couple of months of the pandemic, when there are fewer cases, the analyses will be largely descriptive and focus on percentages and cross tabulations. However, as soon as it is feasible, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) will be calculated for each of the triage tools using different triage tool score thresholds. An example of analysis output is given in table 1. The discriminatory value of existing and refined triage tools will be compared using logistic regression. The performance of different triage tools will be compared on their ability to predict outcome using area under the Receiver Operating Characteristic curve (AUROC) comparisons. An example of analysis output is given in figure 2.

Cumulative analysis will be reset between pandemic waves and appropriate comparisons made between pandemic waves. Analyses can be reset if there is a substantial change to the model of pandemic influenza health care provision such as introduction of an automated National Pandemic Influenza Service which would be likely to alter the case mix presenting to GPs.

Risks / benefits to patients

For the individual patient there are no readily identifiable risks that result from the project. All data is anonymised to allow analysis without compromising patient confidentiality. It is possible that participating GPs

will adapt their consultation practise to conduct clinical assessment in a structured format. This may benefit patients.

Once the study processes are developed and piloted, the methods can be activated to determine the appropriate management of other novel non-influenza severe acute respiratory pathogens e.g. SARS coronavirus.

Risks / benefits to study

We have identified two system specific risks for the proposed study:

1. That despite prompts in the clinical software, that GPs will not enter their assessment in COVID-19 specific eHRS and instead use other free-text fields.
2. It is accepted that there may be up to a week's delay in availability of data from hospital discharge that is dependent upon manual input to eHRS by GPs clerks (e.g. length of stay). There is potential for failure, reduced quality and increased delay of production of discharge faxes at some hospitals due to local pandemic influenza pressures on staff and financial penalties may be lifted. This will be mitigated by the very large size of the study recruiting from practices spread across the UK. This risk is not expected to affect data return for the primary outcome (hospital admission within 24 hours of GP assessment) as this data is returned automatically or notice of death which is handled as a priority to be communicated directly to GPs by clinical staff. Standard operating procedures are in place ensure rapid disseminating of notice of death in primary care systems to prevent inappropriate contacts and distress to bereaved relatives.

Consent

Patient consent is not required as all patient data collected is routine, depersonalised and no intervention is taking place. Anonymised patient data in HES is subject to an NIGB section 251 approval for approved use without consent.

Ethics

GPRD research group has generic ethical approval for studies that only make use of anonymised data and linked anonymised Hospital Episode Statistics. All studies require scientific approval from the GPRD Independent Scientific Advisory Committee (ISAC). This study protocol was be submitted to ISAC for review. In the event that ethical review is required by ISAC, a submission will be made to a Multi-Centre Research Ethics Committee via the Integrated Research Application System.

The National Information Governance Board for Health and Social Care has authorised the Information Centre for Health and Social Care to provide anonymised Hospital Episode Statistics as the official statistical database on NHS hospital activity in England under a section 251 approval.

On 20th March 2020 a general Control of Patient Information notice has been served by the Secretary of Health and Social Care under Regulation 3(4) of the Health Service (Control of Patient Information) Regulations 2002. The purpose of this Notice is to require organisations to process confidential patient information for the purposes set out in Regulation 3(1) of COPI to support the Secretary of State's response to Covid-19 (Covid-19 Purpose). "Processing" for these purposes is defined in Regulation 3(2) and includes dissemination of confidential patient information to persons and organisations permitted to process confidential patient information under Regulation 3(3) of COPI. A Covid-19 Purpose includes but is not limited to the following: research and planning in relation to Covid-19.

Outputs from the study

In Phase one and two, progress reports to the oversight group will be made every three months, with a final report being submitted at the end of phase two to NETSCC and Department of Health Pandemic Influenza Planning Team.

Reports will detail:
In Phase one

- GP involvement in developing data capture screens.
- User acceptability (GP) testing of data capture screens.
- Completeness of data from GPRD based on retrospective analysis using HES-linked GPRD data as a gold standard for data completeness.

In Phase two

- Weekly statistical analysis of cases of seasonal influenza to demonstrate capability of processes and retrospective validation against HES data.

- An accrual graph of patients studied by week number plotted above the HPA Weekly National Influenza Report of GP reported ILI consulting rates in the UK.

During phase three (pandemic), summary results of statistical analysis and recommendations regarding the triage tools will be reported to the oversight committee on a fortnightly basis and shared with the Pandemic Influenza Clinical Operation Clinical Subgroup (PICO) and the Scientific Advisory Group for Emergencies (SAGE). The reporting cycle will be flexible and can be adapted to marry with the battle rhythm of these key sources of advice to policy makers. The research team have a deep understanding of the need to communicate their findings successfully.

Reports will detail:

- An accrual graph of patients studied by week number plotted above the HPA Weekly National Influenza Report of GP reported ILI consulting rates in the UK.
- Results of statistical analysis detailing ROC, Sensitivity, Specificity, PPV, NPV for triage criteria and AUROCs for triage tools against the primary outcomes: hospital admission, higher levels of care (2 – HDU, 3 –ITU) and death.
- Recommendations regarding which criteria and tools to use in the event of surge.

In the post pandemic phase a final report will be produced and manuscripts prepared for publication.

Two of the investigators will present findings at an international conference.

Research governance

The University of Liverpool will act as sponsor for the study.

The proposed study will be undertaken in accordance with the University of Liverpool's research governance procedures.

Dr MG Semple (Liverpool) and Prof Jonathan Van-Tam (Nottingham) will be joint guarantors for analysis and reports.

Study Oversight Committee

A formal steering committee is impractical. A small independent oversight group has already been convened which includes a research active principal in primary care with a particular interest in identification of severe illness in children and a consultant in infectious diseases who is an expert in translating evidence to policy and policy to practice. Both have already made recommendations to the protocol that have been accepted.

Dr Anthony Harnden, Principle in General Practise and Director of Primary care Research Network Clinical (PCRN) Clinical Trials Unit Oxford. Dr Harnden is a member of PICO; appointed as an independent expert clinical advisor in Primary Care. He has published on identifying factors that identify children with serious infection in primary care, avoidable factors associated with chid deaths and the evidence base for interventions delivered to children in primary care.

Dr Barbara Bannister, Consultant in Infectious Diseases, and Consultant Clinical Advisor to Department of Health. Dr Bannister is a member of PICO; appointed as an expert clinical advisor in infectious diseases and as a representative of the DH Pandemic Influenza Programme. Dr Bannister supported the development and communication of operational guidance for medical professionals, including the mass use of antiviral and antibiotic therapy, clinical management guidelines, NPFS algorithms, triage and hospital pathways.

A NIHR NETSCC monitor or representative will be invited to join the group.

In phase one and two the investigators plan to meet with the overseers at least at commencement and at three monthly intervals.

In phase three, weekly reports will be presented to the overseers for ratification before being presented to SAGE, PICO and policy makers in DH.

TIMETABLE & MILESTONES

01/04/2012 – 30/09/2010 Phase one (inter-pandemic – development / feasibility), duration six months during a summer season: set-up and validation of processes, optimisation of the clinical record entry screen in LEPIS, GP acceptability testing, completeness of data, validation of linkage between Vision®, LEPIS, HES and GPRD, data-return format and development of data clean-up algorithms. Progress reports and meeting at 3 and 6 months with overseers.

01/10/2012 – 31/03/2013 Phase two (inter-pandemic – pilot), duration six months in a winter season in 50 practices. Using data from cases of influenza like illness: test data-cleaning algorithms and the automated weekly evaluation of performance of triage criteria and tools. Rehearsal of reporting procedures and reporting rhythm to PICO and SAGE. Progress reports and meeting at 3 and 6 months with overseers. A manuscript for publication will be produced at the completion of phase 2.

Phase three will be activated in the event of a pandemic, duration 12 months. We will run a weekly cumulative analysis, allowing refinement of criteria and tools against the novel pandemic strain in readiness for surge. Monthly summary reports to overseers during pandemic phase. When ready, refined and validated tools will be presented to overseers, seeking approval to reporting to policy makers. Meeting at least at 3, 6, and 9 months to overseers. A manuscript for publication will be produced in the post pandemic period and before month 12.

SERVICE USE INPUT

The NIHR Primary Care Research Network (PCRN) Clinical Study Group have reviewed the study outline.

A principle in primary care (AH member of oversight committee) has reviewed to full protocol.

The GPRD research group and development practices include physicians and principles in General Practice who have an appropriate vested interest in optimising the methods for data entry and developing appropriate triage tools for us in the communities they care for.

DURATION OF THE PROPOSED PROJECT

- **Phase one** (inter-pandemic - development & feasibility). Proposed start date 01.04.2012. Duration six months during a summer season: set-up and validation of processes, optimisation of the clinical record entry screen, GP acceptability testing, validation of linkage to hospital episode data, data-return format and development of data clean-up algorithms.
- **Phase two** (inter-pandemic – pilot), Proposed start date 01.010.2012. Duration six months in 10 to 20 practices during a winter season. Using data from people presenting with of influenza like illness: test data-cleaning algorithms and the automated weekly evaluation of performance of triage criteria and tools. The project will be mothballed at end of phase two.
- **Phase three** will be activated in the event of a pandemic. The duration of a pandemic is hard to estimate. Based on the 2009 event, time from detection of person-to-person spread in the UK to peak activity was three months in the first wave with return to base line activity in a further one month. The second wave had a broader base and longer tail lasting approximately 5 months. The modified GP electronic record will be disseminated to all 629 GPRD practices by the routine update process. Weekly analysis and outputs as described will require increased commitment from all investigators. Costing phase three of the study for one year would allow checks on validity of tools to made between waves; would allow for variations in health seeking behaviour and GP clinical practise between waves, plus a three month wash up period for final analysis and reporting.

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PAEDIATRIC

Swine flu paediatric community assessment tool

For use in all children under 16 years old in the community.

This assessment tool should be used during a pandemic situation to assist with the decision as to whether a sick febrile child with flu-like illness needs referral to the nearest general hospital Emergency Department. The majority of children are expected to be managed in the community.

Respiratory failure, overwhelming gastroenteritis, shock, heart failure and encephalitis are the most likely modes of critical illness in children suffering from swine flu. Complications such as sepsis and meningitis may co-exist.

Criteria label	REFER CHILDREN TO THE NEAREST GENERAL HOSPITAL EMERGENCY DEPARTMENT 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 their own GP or clinical team** e.g. a rapidly progressive or an unusually prolonged illness.

Further information

- This tool is designed to support and empower all healthcare professionals working in difficult circumstances with limited resources, but does not supersede a decision by an experienced clinician about whether, when or where to refer a child.
- The assessment applies to all children under 16 years old and is independent of any prior or existing medical condition.
- **Infants less than 2 months old with increased respiratory rate and sternal recession should be referred promptly to the nearest hospital because they are at high risk of suffering severe illness or death.**
- Fever alone is not used as a criterion for referral to hospital in children over 3 months of age, as it is a poor discriminator for severe illness.
- Difficulty in feeding indicates a need for assessment but is not by itself a good measure of severe illness.
- When referral is not indicated, a copy of the home care advice leaflet should be provided, with encouragement to call again should the child's condition deteriorate.
- Every assessment should include a record of the time of assessment and time of onset of illness. Referrals must include the criteria label(s) to assist with the treatment of children on arrival at hospital.

The Swine Flu Paediatric Community Assessment Tool is endorsed by: The Royal College of General Practitioners, The Royal College of Paediatrics and Child Health, The Royal College of Nursing, The Royal College of Midwives, The College of Emergency Medicine, The Directors of Clinical Care of UK Ambulance Trusts, The British Medical Association and Unite/The Community Practitioners' and Health Visitors' Association.

ADULT

Swine flu adult community assessment tool

For use in all adults aged 16 years or older in the community.

This assessment tool should be used during a pandemic situation to assist with the decision as to whether a sick febrile adult with flu-like illness needs referral to the nearest general hospital Emergency Department. The majority of adults are expected to be managed in the community.

Respiratory failure, shock, heart failure and encephalopathy are the most likely modes of presentation in adults suffering from severe infection.

Criteria label	REFER ADULTS TO THE NEAREST GENERAL HOSPITAL EMERGENCY DEPARTMENT 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 their own GP or clinical team** e.g. a rapidly progressive or an unusually prolonged illness.

Further information

- The tool is designed to support and empower all healthcare professionals working in difficult circumstances with limited resources but does not supersede a decision by an experienced clinician about whether, when or where to refer an adult.
- The assessment applies to all adults aged 16 years or over and is independent of any prior or existing medical condition.
- Fever alone is not used as a criterion for referral as it is a poor discriminator for severe illness.
- Difficulty in self care indicates a need for assessment but is not by itself a good measure of severe illness or need for hospital admission. Referral to a community-based support facility may be suitable.
- When referral is not indicated, a copy of the home care advice leaflet should be provided, with encouragement to seek medical advice again should the adult's condition deteriorate.
- Every assessment should include a record of the time of assessment and time of onset of illness. Referrals must include the criteria label(s) to assist with the treatment of adults on arrival at hospital.

The Swine Flu Adult Community Assessment Tool is endorsed by: The Royal College of General Practitioners, The Royal College of Physicians, The Royal College of Nursing, The College of Emergency Medicine, The Directors of Clinical Care of UK Ambulance Trusts and The British Medical Association.

Figure 1. Paediatric & Adult DH/NHS Community Assessment Tools.

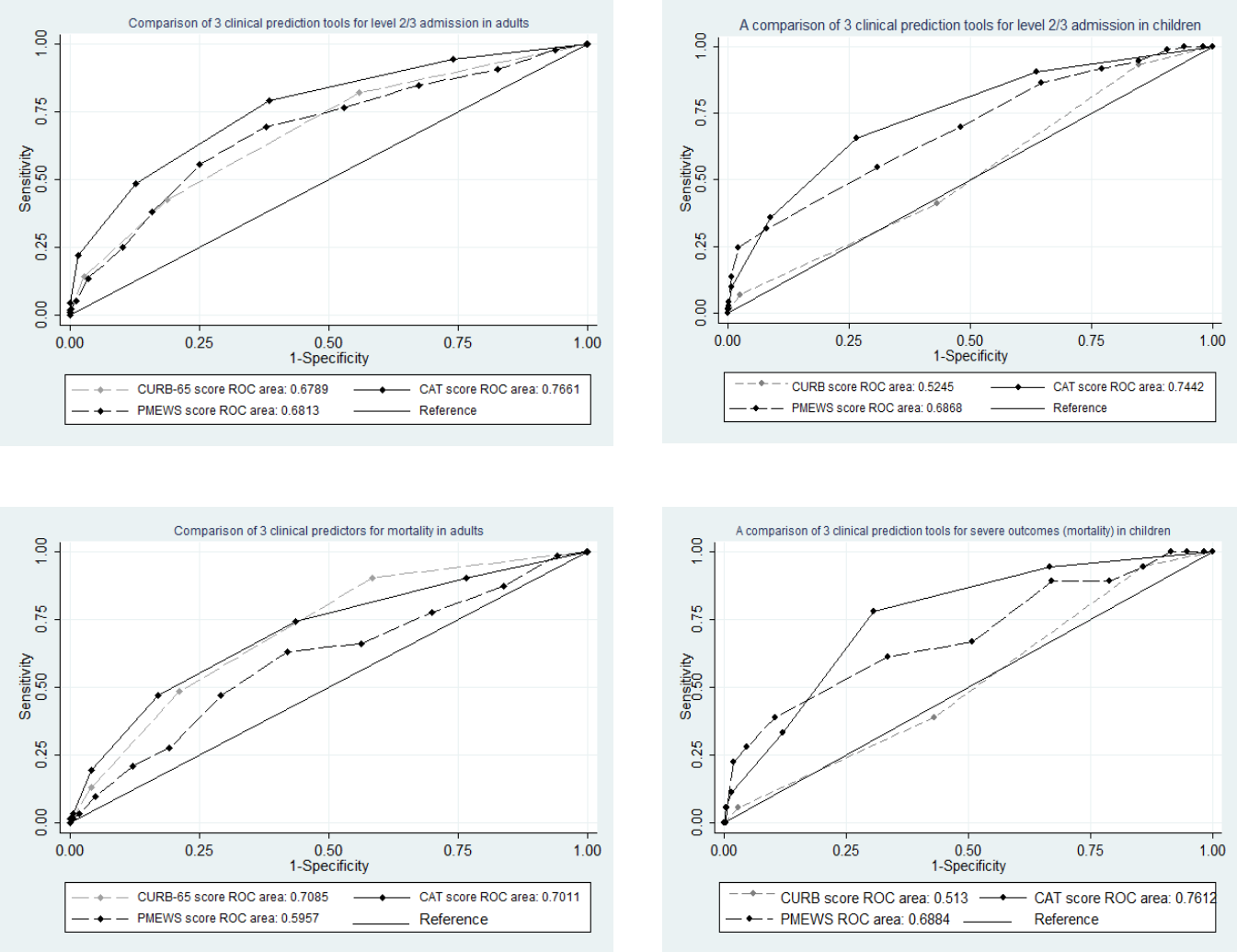

Figure 2: ROC curves comparing the predictive value of CAT scores (solid lines), CURB-65 (grey dashed lines) and PMEWS (black dashed lines) in relation to admission to level 2-high dependency care and level 3 intensive care (upper panels) and mortality (lower panels) in adults (left panels) and children ≤16 years (right panels).

Outcome	Score	ROC area (95% CI)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)
Level 2/3 admission	CURB-65 ≥2	0.62 (0.58, 0.66)	42.4 (35.0, 50.0)	81.2 (78.5, 83.8)	31.6 (25.8, 38.0)	87.3 (84.8, 89.5)
	CURB-65 ≥3	0.56 (0.53, 0.58)	14.1 (9.4, 20.1)	97.2 (95.9, 98.2)	51.0 (36.3, 65.6)	84.7 (82.3, 86.9)
	PMEWS >1	0.52 (0.51, 0.53)	97.7 (94.3, 99.4)	6.3 (4.7, 8.1)	17.6 (15.3, 20.1)	93.1 (83.3, 98.1)
	PMEWS >2	0.54 (0.51, 0.56)	90.4 (85.1, 94.3)	17.4 (14.9, 20.1)	18.3 (15.8, 21.1)	89.8 (84.2, 94.0)
	PMEWS >3	0.54 (0.51, 0.56)	90.4 (85.1, 94.3)	17.4 (14.9, 20.1)	18.3 (15.8, 21.1)	89.8 (84.2, 94.0)
	PMEWS >4	0.59 (0.56, 0.62)	84.7 (78.6, 89.7)	32.6 (29.4, 35.8)	20.5 (17.6, 23.6)	91.2 (87.5, 94.1)
	PMEWS >5	0.62 (0.58, 0.65)	76.3 (69.3, 82.3)	47.0 (43.7, 50.4)	22.8 (19.5, 26.4)	90.6 (87.5, 93.2)
	PMEWS >7	0.65 (0.61, 0.69)	55.4 (47.7, 62.8)	74.9 (71.8, 77.7)	31.1 (26.0, 36.5)	89.1 (86.6, 91.3)
	PMEWS >9	0.57 (0.54, 0.61)	24.9 (18.7, 31.9)	89.7 (87.5, 91.6)	33.1 (25.2, 41.8)	85.3 (82.9, 87.6)
	PMEWS >11	0.52 (0.50, 0.54)	5.1 (2.4, 9.4)	98.7 (97.7, 99.4)	45.0 (23.1, 68.5)	83.5 (81.1, 85.8)
	CAT ≥3	0.68 (0.64, 0.72)	48.6 (41.0, 56.2)	87.3 (84.8, 89.4)	43.9 (36.8, 51.1)	89.2 (86.9, 91.2)
	CAT ≥4	0.60 (0.57, 0.63)	22.0 (16.2, 28.9)	98.4 (97.3, 99.1)	73.6 (59.7, 84.7)	86.0 (83.7, 88.1)
	CAT ≥5	0.52 (0.51, 0.54)	4.5 (2.0, 8.7)	100.0 (99.6, 100.0)	100.0 (63.1, 100.0)	83.6 (81.2, 85.8)
Death	CURB-65 ≥2	0.64 (0.57, 0.70)	48.4 (35.5, 61.4)	78.8 (76.1, 81.4)	12.7 (8.7, 17.6)	96.0 (94.4, 97.3)
	CURB-65 ≥3	0.54 (0.50, 0.59)	12.9 (5.7, 23.9)	95.8 (94.4, 97.0)	16.3 (7.3, 29.7)	94.6 (92.9, 95.9)
	PMEWS >1	0.52 (0.50, 0.54)	98.4 (91.3, 100.0)	5.8 (4.4, 7.5)	6.2 (4.8, 7.9)	98.3 (90.8, 100.0)
	PMEWS >2	0.52 (0.47, 0.56)	87.1 (76.1, 94.3)	16.3 (14.0, 18.7)	6.2 (4.7, 8.0)	95.2 (90.8, 97.9)
	PMEWS >3	0.52 (0.47, 0.56)	87.1 (76.1, 94.3)	16.3 (14.0, 18.7)	6.2 (4.7, 8.0)	95.2 (90.8, 97.9)
	PMEWS >4	0.54 (0.48, 0.59)	77.4 (65.0, 87.1)	30.1 (27.2, 33.0)	6.6 (4.9, 8.6)	95.5 (92.5, 97.5)
	PMEWS >5	0.55 (0.49, 0.61)	66.1 (53.0, 77.7)	43.7 (40.5, 46.8)	6.9 (5.0, 9.3)	95.3 (92.9, 97.1)
	PMEWS >7	0.59 (0.52, 0.65)	46.8 (34.0, 59.9)	70.8 (67.8, 73.6)	9.2 (6.3, 13.0)	95.4 (93.7, 96.8)
	PMEWS >9	0.54 (0.49, 0.60)	21.0 (11.7, 33.2)	87.7 (85.5, 89.7)	9.8 (5.3, 16.1)	94.6 (92.9, 96.0)
	PMEWS >11	0.51 (0.48, 0.53)	3.2 (0.4, 11.2)	98.2 (97.1, 98.9)	10.0 (1.2, 31.7)	94.1 (92.5, 95.5)
	CAT ≥3	0.65 (0.58, 0.71)	46.8 (34.0, 59.9)	82.9 (80.4, 85.2)	14.8 (10.1, 20.6)	96.1 (94.6, 97.3)
	CAT ≥4	0.58 (0.53, 0.63)	19.4 (10.4, 31.4)	95.8 (94.4, 97.0)	22.6 (12.3, 36.2)	94.9 (93.4, 96.2)
	CAT ≥5	0.51 (0.49, 0.54)	3.2 (0.4, 11.2)	99.4 (98.7, 99.8)	25.0 (3.2, 65.1)	94.2 (92.6, 95.5)
Combined severe outcome (level 2/3 admission or death)	CURB-65 ≥2	0.63 (0.59, 0.66)	43.5 (36.3, 50.8)	81.9 (79.1, 84.4)	35.0 (29.0, 41.5)	86.6 (84.0, 88.8)
	CURB-65 ≥3	0.56 (0.53, 0.58)	14.1 (9.5, 19.9)	97.4 (96.1, 98.4)	55.1 (40.2, 69.3)	83.5 (81.0, 85.7)
	PMEWS >1	0.52 (0.51, 0.53)	97.9 (94.7, 99.4)	6.4 (4.8, 8.2)	19.0 (16.6, 21.6)	93.1 (83.3, 98.1)
	PMEWS >2	0.53 (0.51, 0.56)	89.5 (84.3, 93.5)	17.3 (14.8, 20.0)	19.6 (17.0, 22.4)	88.0 (82.1, 92.5)
	PMEWS >3	0.53 (0.51, 0.56)	89.5 (84.3, 93.5)	17.3 (14.8, 20.0)	19.6 (17.0, 22.4)	88.0 (82.1, 92.5)
	PMEWS >4	0.58 (0.55, 0.61)	83.2 (77.2, 88.2)	32.5 (29.4, 35.8)	21.7 (18.8, 24.9)	89.6 (85.7, 92.8)
	PMEWS >5	0.61 (0.57, 0.65)	74.9 (68.1, 80.9)	47.1 (43.7, 50.5)	24.2 (20.8, 27.8)	89.3 (86.0, 92.0)
	PMEWS >7	0.64 (0.60, 0.68)	53.4 (46.1, 60.6)	74.9 (71.9, 77.8)	32.4 (27.2, 37.9)	87.7 (85.1, 90.0)
	PMEWS >9	0.57 (0.53, 0.60)	23.6 (17.7, 30.2)	89.6 (87.4, 91.6)	33.8 (25.9, 42.5)	83.9 (81.3, 86.2)
	PMEWS >11	0.52 (0.50, 0.54)	5.2 (2.5, 9.4)	98.8 (97.8, 99.4)	50.0 (27.2, 72.8)	82.3 (79.8, 84.6)
	CAT ≥3	0.68 (0.64, 0.72)	48.2 (40.9, 55.5)	87.8 (85.4, 89.9)	46.9 (39.8, 54.2)	88.3 (85.9, 90.4)
	CAT ≥4	0.60 (0.57, 0.63)	21.5 (15.9, 28.0)	98.6 (97.5, 99.3)	77.4 (63.8, 87.7)	84.8 (82.4, 87.0)
	CAT ≥5	0.52 (0.51, 0.54)	4.2 (1.8, 8.1)	100.0 (99.6, 100.0)	100.0 (63.1, 100.0)	82.3 (79.8, 84.6)

Table 1: Predictive value of CAT scores, CURB-65 and PMEWS for predicting severe outcomes in adults (≥16 years), n=1040.

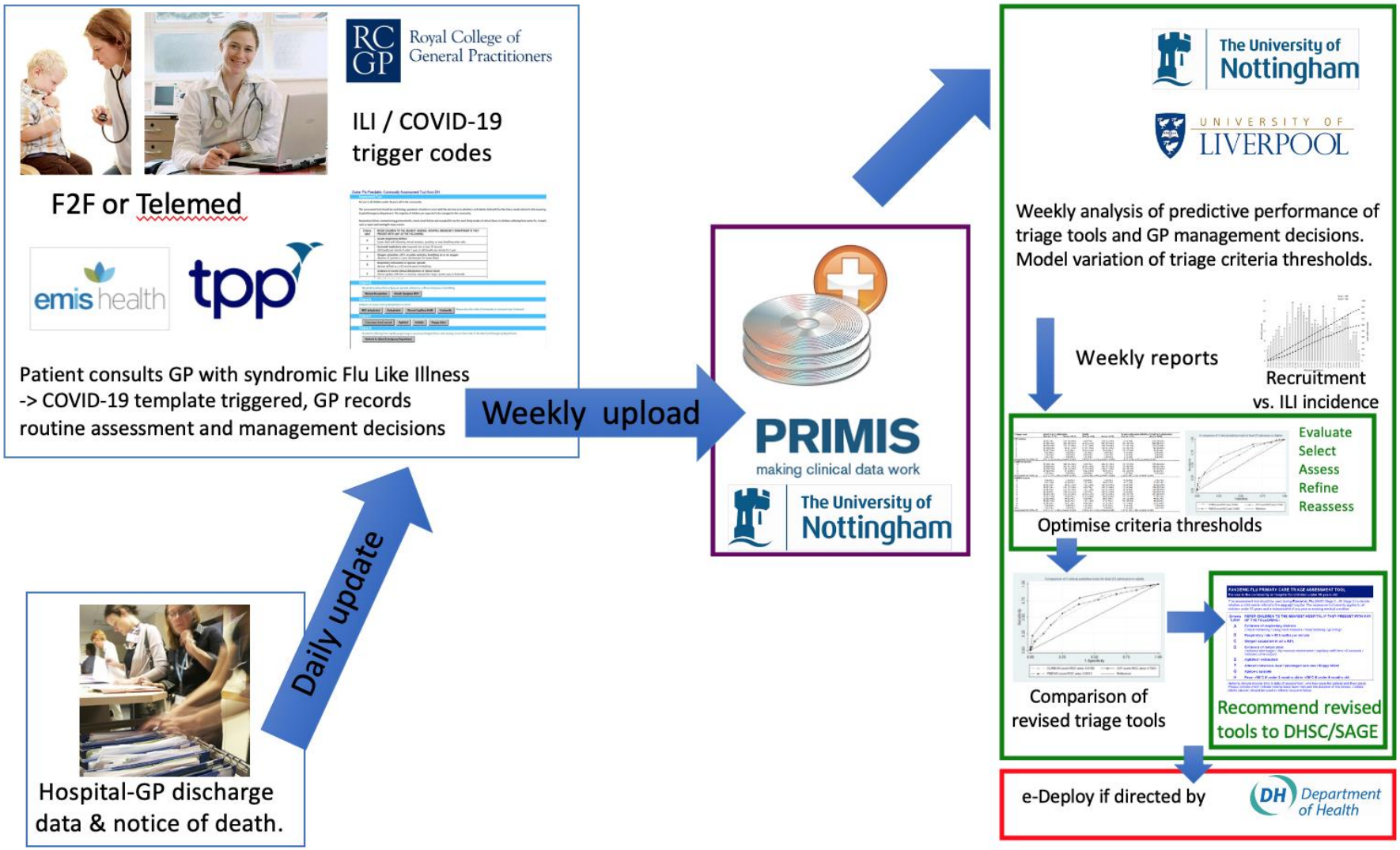

Figure 3. Cartoon of data flow

Protocol Revision

Changes made from version 1 to version 2.

Page & Section	**Change**	**Justification**
General	Removal of reference to GPRD where appropriate	GPRD no longer providing data, Administrative
General	Insertion of EMIS and SystmOne where appropriate	EMIS and SystmOne are now providing data, Administrative
P1 Summary	Updated to reflect emergence of COVID-19. Updated to clarify contemporary use of telemedicine in context of emergence of COVIC-19 Adaptation to clarify relevance to COVID-19 event and policy.	Administrative as COVID-19 presents with syndromic influenza like illness.
P1 Summary	Update of Co-Investigators	Administrative
P1 Summary	Change of data providers	Administrative
P2 Timeline	Clarification of roles of data providers	Administrative
P4 Justification	Removal of linkage to HES	Administrative
P4 Justification	Updated to reflect emergence of COVID-19.	Administrative
P4 Primary objective	Update of advisory groups	Administrative
P5 Secondary Objectives	Clarification that study is relevant to COVID-19	Administrative
P5 Plan of study	Change of data providers	Administrative
P7 Inclusion and Exclusion criteria	Clarification that study is relevant to COVID-19. Clarification that study will collect data from GP consultations including those at walk-in-centres and hot-clinics	Administrative
P7 Data Sources	Recognition that GPRD no longer provide data	Administrative
P8 Data Sources	Recognition that EMIS and SystmOne are now data providers	Administrative
P11 Ethics	Recognition that a COPI notice is in place for the COVID-19 event	Administrative

END