NCCHTA

09 May 2007

STUDY PROTOCOL

Randomised controlled trial to evaluate impact of diagnostic testing for influenza, respiratory syncytial virus and *Streptococcus pneumoniae* infection on the management of acute admissions in the elderly and high-risk 18-64-year olds

Funder ref No. 03/39/18

Principal investigator

Professor Karl G Nicholson**,**
Infectious & Tropical Diseases Unit,
Leicester Royal Infirmary,
Infirmary Square,
Leicester LE1 5WW, England

Telephone - 0116 2586164
Facsimile - 0116 2585067
e-mail – karlgnicholson@doctors.org.uk

Co-investigators

1. Professor MR Barer,
Professor of Clinical Microbiology & Hon Consultant,
Medical Sciences Building,
University Road,
Leicester LE1 9HN

Tel: 0116 252 2933
Fax: 0116 252 5030
e-mail – mrb19@le.ac.uk

2. Dr Maria Zambon,
HPA Enteric, Respiratory & Neurological Virus Laboratory
61 Colindale Avenue
London NW9 5HT

Tel: 0208 200 4400 ext 3239, 3255
Fax: 0208 205 8195
e-mail – maria.zambon@hpa.org.uk

3. Dr Robert George,
HPA Respiratory and Systemic Infection Laboratory
61 Colindale Avenue
London NW9 5HT

Tel: 0208 200 4400 ext 4222
Fax: 0208 205 6528
e-mail – robert.george@hpa.org.uk

4. Dr Alison Bermingham,
HPA Enteric, Respiratory & Neurological Virus Laboratory

61 Colindale Avenue
London NW9 5HT

Tel: 0208 200 4400 ext 3217
Fax: 0208 205 8195
e-mail – alison.bermingham@hpa.org.uk

5. Dr Kumar Rajakumar,
Medical Sciences Building, PO Box 138
University Road
Leicester LE1 9HN

Tel: 0116 223 1498
Fax: 0116 252 5030
e-mail – kr46@le.ac.uk

6. Dr Tim Harrison,
HPA Atypical Pneumonia Unit
61 Colindale Avenue
London NW9 5HT

Tel: 0208 200 4400
Fax: 0208 205 6528
e-mail – tim.harrison@hpa.org.uk

7. Mr David Turner,
Department of Health Sciences
22-28 Princess Road West
Leicester LE1 6TP

Tel: 0116 252 5436
Fax: 0116 252 5423
e-mail – dat3@leicester.ac.uk

8. Professor Keith Abrams,
Department of Health Sciences
22-28 Princess Road West
Leicester LE1 6TP

Tel: 0116 252 3217
e-mail – keith.abrams@le.ac.uk

9. Dr Michael Steiner,
Glenfield Hospital
Leicester

Tel: 0116 287 1471
Fax: 0116 258 3950
e-mail – michael.steiner@uhl-tr.nhs.uk

10. Dr Maria Fraser,
Department of Microbiology
Leicester Royal Infirmary
Leicester LE1 5WW

Tel: 0116 2586516 (mob 07740924692)
Fax: 0116 2551949
e-mail – maria.fraser@uhl-tr.nhs.uk

11. Professor Peter Andrew,

Medical Sciences Building,
University Road,
Leicester LE1 9HN

Tel: 0116 252 2941
Fax: 0116 252 5030
e-mail – pwa@leicester.ac.uk

12. Dr Iain Stephenson,
Infectious & Tropical Diseases Unit,
Leicester Royal Infirmary,
Infirmary Square,
Leicester LE1 5WW, England

Tel: 0116 2586952
Fax: 0116 2585067
e-mail – iain.stephenson@uhl-tr.nhs.uk

13. Mrs S Batham,
Room 0/119 Clinical Research Centre
Level 0, Balmoral Building
Leicester Royal Infirmary.

Tel: 0116 2585973
Fax: 0116 2585973
e-mail – seb38@leicester.ac.uk

Sponsor NHS R&D National Coordinating Centre for Health Technology
Wessex Institute for Health Research & development
Mailpoint 728, Boldrewood,
University of Southampton
Southampton SO16 7PX

Tel: 0238 059 5586
Fax: 0238 059 5639

Date 26/11/2007 Version 6

PROTOCOL SYNOPSIS

Title	Randomised controlled trial to evaluate impact of diagnostic testing for influenza, respiratory syncytial virus and Streptococcus pneumoniae infection on the management of acute admissions in the elderly and high-risk 18-64-year-olds.
Sponsor	NHS R&D National Coordinating Centre for Health Technology Assessment
Study population	Male or female elderly (≥65 years old) patients, Male or female patients aged ≥18 years with underlying heart or lung disease including asthma , or pneumonia / influenza type symptoms**.**
Study setting	Medical Admissions Units in the University Hospitals of Leicester NHS Trust (Leicester Royal Infirmary, Glenfield Hospital, Leicester General Hospital).
Duration	August 1 2005- July 31 2008 (36m). Patient enrolment will occur during: September 1 2005 to June 30 2006; September 1 2006 to June 30 2007; & September 1 2007 to June 30 2008 All patients will be followed-up for 28 days.
Rationale	The purpose of this study is to determine the diagnostic accuracy and clinical- and cost-effectiveness of rapid molecular and near patient diagnostic tests for influenza, RSV and *S. pneumoniae* infections in the elderly, and subjects aged ≥18 years with chronic cardiopulmonary conditions, or pneumonia / influenza type symptoms. in comparison to traditional laboratory culture.
Objectives and hypotheses	**Research objectives:** 1. To determine the diagnostic accuracy (sensitivity, specificity, positive and negative predictive values) of rapid molecular and near patient diagnostic tests for influenza, RSV and *S. pneumoniae* infections in comparison to traditional laboratory culture. 2. To assess the potential benefits of ease of use, and speed of rapid molecular and near patient diagnostic tests for influenza, RSV and *S. pneumoniae* infections, in comparison to traditional laboratory culture. 3. To determine whether rapid molecular and near patient diagnostic tests for influenza, RSV and *S. pneumoniae* infections have any impact on the prescription of antimicrobials. 4. To determine whether rapid molecular and near patient diagnostic tests for influenza, RSV and *S. pneumoniae* infections allow more appropriate use of isolation facilities, in comparison to traditional laboratory culture. 5. To compare the costs of performing rapid molecular and near patient diagnostic tests for influenza, RSV and *S. pneumoniae* infections, in comparison to traditional laboratory culture. 6. To assess cost-savings associated with earlier use of narrow-spectrum antimicrobial therapy (or avoidance or discontinuation of antibiotics) in patients whose influenza, RSV and *S. pneumoniae* infections are diagnosed more rapidly by rapid molecular and near patient diagnostic tests, in comparison to traditional laboratory culture. 7. To compare the outcome of patients whose influenza, RSV, and *S. pneumoniae* is diagnosed more rapidly by rapid molecular and near patient diagnostic tests, compared to those who are diagnosed by traditional laboratory culture.

8. To assess the impact that rapid molecular and near patient diagnostic tests have on the costs associated with an inpatient stay and on costs post-discharge up to a maximum of 28 days after admission.
9. To assess the impact that rapid molecular and near patient diagnostic tests have on quality-of-life, as measured by the EuroQol, and to use this information to estimate the quality adjusted life years (QALYs) generated during the 28 days after admission.
10. To assess the cost-effectiveness of rapid molecular and near patient diagnostic tests in comparison to traditional laboratory culture. This will be done on the basis of both cost per case detected and cost per QALY.
11. **To explore whether patients with pneumococcal infection have lower levels of cellular and humoral immunity to the pnuemococcus in comparison to patients who do not have pneumococcal infection.**

Hypotheses:

1. The increased diagnostic accuracy of rapid molecular and near patient tests over traditional laboratory methods improves patient management through better use of antimicrobials and isolation facilities. Rapid molecular and near patient diagnostic tests for influenza, RSV and *S. pneumoniae* infections are more cost-effective than traditional laboratory diagnostic tests.
2. Rapid molecular and near patient diagnostic tests for influenza, RSV and *S. pneumoniae* infections provide benefits in terms of (a) ease of use, and (b) more rapid results, in comparison to traditional laboratory culture.
3. Rapid molecular and near patient diagnostic tests for influenza, RSV and *S. pneumoniae* infections result in earlier use of 'narrow-spectrum' antimicrobial therapy; an earlier switch from intravenous to oral therapy; and earlier discontinuation of antibiotics in patients infected with influenza and RSV - in comparison to traditional laboratory culture
4. Rapid detection of influenza and RSV by rapid molecular and near patient diagnostic tests leads to the appropriate isolation of patients, but only in hospitals/wards having an adequate provision of cubicles.
5. The costs of performing rapid molecular and near patient diagnostic tests for influenza, RSV and *S. pneumoniae* infections, differ significantly from the cost of traditional laboratory culture.
6. The earlier use of narrow-spectrum antimicrobial therapy (or avoidance or discontinuation of antibiotics) in patients whose influenza, RSV and *S. pneumoniae* infections are diagnosed more rapidly by rapid molecular and near patient diagnostic tests results in significant cost-savings, in comparison to traditional laboratory culture.
7. A streamlining of antimicrobial prescribing that may arise from more rapid diagnosis of influenza, RSV and *S. pneumoniae* infections by rapid molecular and near patient diagnostic tests does not adversely affect patient outcome.
8. Any increase in costs incurred by rapid molecular and near patient diagnostic tests, in comparison to traditional laboratory culture, are more than offset by savings that arise from either rational antimicrobial prescribing or earlier discharge from the hospital.
9. Rapid molecular and near patient diagnostic tests result in an improvement in quality-of-life, as measured by the EuroQol, which arises from streamlining of antibiotics and earlier discharge into the community.
10. Rapid molecular and near patient diagnostic tests are more cost-effective than traditional laboratory culture.
11. **Patients with pneumococcal infections have lower levels of cellular and humoral immunity to the pneumococcus in comparison to patients who do not have pneumococcal infection**

Observational objectives:

1. To estimate the admission rates for influenza, RSV, and *S pneumoniae* in the target population.

2. To compare the clinical characteristics and economic burden of influenza A and B and RSV A and B.
3. To review the implications of rapid diagnosis on isolation policy, and review alternate approaches to managing the infection control issues.

Hypotheses (observational):

1. The admission rates in the target population are higher for *S pneumoniae* than influenza A and B. The admission rates for influenza A and B are similar to those for RSV A and B.
2. The clinical characteristics and economic burden of influenza A and B and RSV A and B are similar.
3. Rapid near patient and/or molecular diagnostic tests will reveal more cases of influenza and RSV who require isolation than can be isolated. Alternate approaches to managing the infection control issues, such as the use of influenza neuraminidase inhibitors, may be pertinent.

METHODOLOGY

Study design	Prospective, randomised controlled trial of the impact of diagnostic testing [(i) Group 1: Rapid near patient diagnostic tests (influenza and pneumococcus), (ii) Group 2: Rapid molecular tests (influenza and RSV), plus laboratory pneumococcal antigen testing, and (iii) Group 3: Traditional 'laboratory culture' (influenza, RSV, and *S. pneumoniae*)] in elderly (≥65 years) and 'high-risk' patients, who present to Medical Admissions' Units in Leicestershire with an acute cardio-pulmonary illness. All tests will eventually be done on all patients who enter the study, but patients in Groups 1 and 2 will only be provided with rapid test results relating to their randomisation group.
Number of cases	***Elderly*** Estimated 2752 cases of acute cardio-pulmonary illness in the elderly, of whom 664 will have pneumonia (J12.9-J18.9). An estimated 556 will have unspecified acute lower respiratory tract infections (J22.X). About one third of the pneumonia cases will have *S. pneumoniae* infections (n=221); If ~5% of all acute cardiopulmonary admissions have laboratory-confirmed RSV and ~10% have influenza, then ~138 cases of RSV and ~275 cases of influenza would be studied in the elderly. ***High-risk 18 to 64-year-olds.*** An estimated 83 cases of pneumonia, with one-third (n=28) having *S. pneumoniae* infections. An estimated 93 cases of unspecified acute lower respiratory tract infections (J22.X); 29 acute unspecified URTI's (J06.9); and 181 cases of COPD. If ~5% of these admissions (n=386) have laboratory-confirmed RSV and ~10% have influenza, then ~19 cases of RSV and ~38 cases of influenza would be studied in 18 to 64 year-old high-risk patients.
Demographic data	· Male or female elderly, aged ≥65 years of age · Male or female 'high-risk' patients with underlying heart or lung conditions, aged 18 to 64 years of age, or with Pneunmonia or influenza like symptoms.
Inclusion criteria	· Able and willing to give written informed Consent, OR a relative or carer is willing to give written informed Assent for patients who are too debilitated to provide consent; · Age ≥65 years, OR age ≥18 years with underlying chronic heart or lung disease including asthma; Or with Pneumonia or influenza like symptoms.

- Have an acute exacerbation of chronic cardio-pulmonary illness of ≤168 hours (7 days) duration, OR an acute cardio-pulmonary illness or influenza-like illness of ≤7 days duration, including:
  - Pneumonia,
  - Influenza/influenza-like illness,
  - Exacerbations of chronic obstructive pulmonary disease (COPD),
  - Bronchitis,
  - Asthma,
  - Congestive heart failure,
  - Cardiac arrhythmia;
- Able and willing to adhere to the procedures stated in the protocol
- Patients should have access to a telephone

Exclusion criteria

- Inclusion criteria not met
- Angina/suspected myocardial infarction;
- Were recruited to this study within 28 days of the current admission
- Could not be recruited into the study within a **16**-hour period of initial assessment by a doctor on the Medical Admissions Unit or a ward accepting acute medical admissions;
- Enrollment in a study of antimicrobial therapy for the illness for which the patient was admitted

---

Randomisation:

Patients in each centre will be randomly allocated to one of three diagnostic policy groups:
Group 1: Near patient tests (Quidel – influenza; Binax NOW – pneumococcus);
Group 2: rapid molecular tests ('flu & RSV plus laboratory testing of concentrated urine in the Binax NOW assay); and
Group 3: traditional laboratory culture,
using computer generated randomisation codes stratified by centre.

Assessment methods:

Clinical

1. Impact of test result on prescribing, specifically:-
   (a) Earlier use of 'narrow-spectrum' anti-microbial therapy,
   (b) Earlier switch from intravenous to oral therapy,
   (c) Avoidance or earlier discontinuation of antibiotics in patients infected with influenza and RSV, and
   (d) Prescriptions of influenza neuraminidase inhibitors

   Will be assessed in rapid near patient (Group 1) and molecular diagnostic groups (Group 2) and compared to traditional laboratory culture (Group 3).

2. Clinical outcomes, specifically:-
   (a) Length of hospital stay;
   (b) Fever duration,
   (c) Supplemental oxygen dependence and CPAP dependence,
   (b) Admissions to Intensive Care,
   (c) Ventilatory support, and
   (d) Deaths

   Will be assessed in rapid near patient (Group 1) and molecular diagnostic groups (Group 2) in comparison to traditional laboratory culture (Group 3).

   Duration of hospitalisation, until discharge or death, will be obtained from the UHL Leicester hospital activity analysis (i.e., from computerised records).

Fever duration The participants' temperature charts will be monitored during the first 10 days of hospitalisation to identify when they first became apyrexial (temperature $\leq$37.2^{o}C), and remained so for a period of at least 24 hours.

Supplemental oxygen dependence and CPAP dependence The participants' will be monitored during the first 10 days of hospitalisation to identify when they no longer required oxygen for a period of at least 24 hours.

Admission to Intensive care, and *Ventilatory support* – during the first 10 days of hospitalisation will be identified and documented by the study nurse in the Case Report Form.

Deaths – that occur within a maximum of 28 days of hospitalisation will be identified and documented by the study nurse in the Case Report Form.

3. Quality of life, as measured by EuroQol, and quality adjusted life years generated during the 28 days after admission will be assessed in rapid near patient (Group 1) and molecular diagnostic groups (Group 2) in comparison to traditional laboratory culture (Group 3).

4. Appropriate use of isolation facilities The time from admission to the Medical Admissions Unit to the time of admission into a single room (isolation cubicle) will be assessed in patients with confirmed influenza and RSV in the rapid near patient (Group 1) and molecular diagnostic groups (Group 2) in comparison to traditional laboratory culture (Group 3).
   The study nurse will document in the CRF where the patient was nursed throughout the first 7 days of admission.

5. Discharge diagnoses – will be obtained from the UHL Leicester hospital activity analysis (i.e., from computerised records).

Financial

6. Costs of diagnostic tests, estimated by means of an 'ingredients' approach where all items needed to carry out the test are recorded and costed using appropriate local and national data, e.g., items to collect and transport specimens, media and reagents for the test, equipment to process specimens, technical support costs, etc. Costs will be identified for the following technologies:
   (a) Rapid near patient test for influenza (Quidel),
   (b) Rapid near patient test for pneumococcus (Binax NOW),
   (c) Molecular (multiplex PCR) tests for influenza A and B and RSV A and B,
   (d) 'Prompt' antigen detection test for pneumococcus (Binax NOW), using x25 concentrated urine in the laboratory,
   (e) Culture (blood and sputum) for *S. pneumoniae,*
   (f) Gram staining of sputum samples,
   (g) Cell culture for influenza A and B,
   (h) Cell culture for RSV A and B,
   (i) Other tests that may be applied, eg immunofluorescence

7. Care costs Cost of inpatient stay will be determined using information on length of stay and hospital costs to determine a 'hotel' cost of routine care. To this will be added the cost of any additional clinical care received such as diagnostic tests, drugs, etc. For patients who are discharged within 28 days of admission, health care resource use in the period after discharge will be recorded using a simple questionnaire administered in a telephone interview. These will be costed using appropriate national data, for example NHS

reference costs unit costs compiled by the PSSRU at the University of Kent.

8. Cost-savings, which accrue from (i) a reduction in the use of resources; and (ii) earlier discharge from the hospital, will be identified by comparison of the costs for participants in Groups 1, and 2, compared to traditional laboratory culture (Group 3).

9 Economic evaluation of near patient and rapid molecular diagnostic tests will be assessed by two main outcomes measures –
(a) cost per case detected,
(b) cost per QALY

Laboratory

10. Diagnostic accuracy, (sensitivity, specificity, positive and negative predictive values) and discrepant analysis of near patient and molecular diagnostic tests, will be estimated in comparison with traditional and other (e.g., serology) laboratory tests.

11. Ease of use of rapid near patient and molecular tests The ease of use of molecular, near patient, and traditional laboratory culture will scored independently by three investigators in terms of whether they can be done:
    - On site,
    - Require special laboratory facilities,
    - Require special equipment,
    - The number of reagents required,
    - The number of steps,
    - Ease of disposal/decontamination of used equipment and reagents,
    - Technical competency required of the operator,
    - Training period required to reliably carry out the test, and any
    - Health and safety implications

12. Speed of tests, Will be assessed in terms of the median time from specimen collection to result:-
    - Appearing in the case notes
    - Appearing on Pathology Department results' database (APEX), and/or
    - Being phoned to the ward
    - Being acted upon - in comparison to traditional laboratory culture.

13. **Anti-neuraminidase, anti-pneumolysin and 1gG antibody in sera and anti-pneumolysin and anti-neuraminidase induced CD4 T-cell activation and**

proliferation profiles from CD4 cells collected from peripheral blood.

Observational

14. Admission rates, For influenza, RSV, and *S pneumoniae* in the target population, taking into consideration the total population estimates, stratified by age, and the proportion of all patients by ICD code that were sampled.

Study procedures

Baseline (Day 1)

- Written informed consent from patient or assent from relative or carer,
- Inclusion/exclusion criteria,
- Randomisation,
- Basic demography,
- Medical history/regular medication,
- Presenting symptoms and the interval between their onset and admission,
- Clinical findings,
- Quality of Life assessment and MRC Dyspnoea Scale.
- Investigations ordered by the admitting physicians
- Specimen collection (blood for antibody tests, sputum, nasopharyngeal specimen, and urine) for trial specific diagnostic tests,
- Rapid near patient diagnostic testing for influenza & pneumococcus (Group 1) on, or adjacent to, the ward. Results will be delivered to the nursing and/or medical team on the MAU and entered into the case notes. The time when the results were entered into the case notes will be recorded in the patient's CRF together with the results,
- Processing and transport of specimens to the laboratory of diagnostic specimens (Groups 1, 2, 3),
- Antimicrobial and antiviral treatments prescribed/dose/frequency/route,
- Isolation status

Information relating to the above activities will be documented in the CRF.

Follow-up (Days 2, 3, 4,5,6, 7,8,9, 10, and 28)

The following will be performed, updated and recorded in the CRF.

- Time when diagnostic tests were made available to the nursing/medical staff,
- Treatment, specifically the relationship between the timing/availability of diagnostic tests and changes in antimicrobial therapy. The nature of treatment given to all patients within 10 days of admission will be documented,
- Isolation, specifically the relationship between the timing/availability of diagnostic tests and changes in isolation status. The isolation status of all patients throughout the first 7 days of admission will be carefully documented,
- Admission to ITU and ventilatory support (within 28 days of hospitalisation),
- Pyrexia – the timepoint when the patient first became apyrexial ($\leq$37.2^{o}C), and remained so for >24 hours (during days 1-10)
- Oxygen requirement – the timepoint when supplemental oxygen was no longer required, and was not given for >24 hours (during days 1-10)
- Diagnostic studies (within 28 days of hospitalisation)

- Duration of hospitalisation
- Deaths (within 28 days of hospitalisation)
- EuroQol (Days 7 and 28)
- Discharge diagnosis
- Convalescent serum sample (Day 10 –90)

Endpoints:

Clinical

1. Impact of test result on prescribing, specifically:-
   (a) Time, from admission to MAU, to first administration of 'narrow-spectrum' antibiotics, for patients in Groups 1, 2, and 3, who are prescribed antibiotics,
   (b) Time, from admission to MAU, to first administration of oral antibiotics, for patients in Groups 1, 2, and 3, who are prescribed antibiotics,
   (c) Time (hours) from admission to MAU to prescription of 'no antibiotics' (oral or intravenous) administered to patients in Groups 1, 2, and 3, who have influenza or RSV, and
   (d) Proportion of patients with influenza in Groups 1, 2, and 3 who are prescribed neuraminidase inhibitors.

2. Clinical outcomes, specifically:-
   (a) *Length of hospital stay* until discharge:
   First, for all patients in Groups 1, 2, and 3.
   Second, for all patients with (i) influenza; (ii) RSV; and (iii) *S. pneumoniae* infection in Groups 1, 2, and 3.
   (b) *Fever duration* (during the first 10 days of hospitalisation) Time from admission (hours) until the patient first became apyrexial (temperature $\leq$37.2^{o}C), and remained so for a period of at least 24 hours:
   First, in all patients in Groups 1, and 2 in comparison to Group 3.
   Second, in patients with *S. pneumoniae* in Groups 1, and 2, in comparison to Group 3.
   (c) *Supplemental oxygen dependence and CPAP dependence* (during the first 10 days of hospitalisation) Times from admission (hours) until the patient required (i) no supplemental oxygen, and (ii) no CPAP, for a period of at least 24 hours:
   First, in all patients in Groups 1, and 2 in comparison to Group 3.
   Second, in patients with *S. pneumoniae* in Groups 1, and 2, in comparison to Group 3.
   (d) *Admissions to Intensive Care* (during the first 10 days of hospitalisation):
   First, the proportion of patients with *S. pneumoniae* infection in Groups 1, 2, and 3.
   Second, to better define the burden of influenza and RSV, the proportion of all patients with (i) influenza, and (ii) RSV who require ITU support.
   (e) *Ventilatory support* (during the first 10 days of hospitalisation):
   First, the proportion of patients with *S. pneumoniae* infection in Groups 1, 2, and 3.
   Second, to better define the burden of influenza and RSV, the proportion of all patients with (i) influenza and (ii) RSV who require ventilatory support.
   (f) *Deaths* (within 28 days of hospitalisation):
   First, the proportion of patients with *S. pneumoniae* infection in Groups 1, 2, and 3.

Second, to better define the burden of influenza and RSV, the proportion of all patients with (i) influenza, and (ii) RSV, who die.

3. Quality of life, as measured by EuroQol, and quality adjusted life years generated during the 28 days after admission, will be assessed:
   (a) In all patients in Groups 1, and 2 in comparison to Group 3.
   (b) Second, in patients in patients with (i) influenza, (ii) RSV, and (iii) *S. pneumoniae* in Groups 1, and 2, in comparison to Group 3.

4. Use of isolation facilities
   (a) The time from admission to the MAU to the time of admission to a single room (isolation cubicle) will be compared for patients with confirmed influenza or RSV in Groups 1, 2, and 3.
   (b) The proportion of patients with influenza or RSV in Groups 1, 2, and 3 who are isolated at any stage during the first 120 hours of the admission.
   (c) The proportion of patients with *S. pneumoniae* infection in Groups 1, 2, and 3 who are inappropriately isolated for >12 hours.

Financial

5. Costs of diagnostic tests, Costs will be identified for:
   (a) Rapid near patient test for influenza (Quidel);
   (b) Rapid near patient test for pneumococcus (Binax NOW),
   (c) Molecular (multiplex PCR) tests for influenza A and B and RSV A and B
   (d) 'Prompt' antigen detection test for pneumococcus (Binax NOW), using 20ml concentrated urine in the laboratory
   (e) Culture (blood and sputum) for *S. pneumoniae*
   (f) Gram staining of sputum samples
   (g) Cell culture for influenza A and B
   (h) Cell culture for RSV A and B
   (i) Other tests that may be applied, eg immunofluorescence

6. Care costs Cost of inpatient stay (± 95%CI) will be determined for:
   (a) All patients in Groups 1, 2, and 3;
   (b) All patients (in all groups) with (i) influenza, (ii) RSV, and (iii) *S. pneumoniae* infection, and
   (c) Patients with (i) influenza, (ii) RSV, and (iii) *S. pneumoniae* infection in Groups 1, 2, and 3,

   For patients who are discharged within 28 days of admission, health care resource use in the period after discharge will be recorded using a simple questionnaire administered in a telephone interview or by post**.**

7. Cost-savings that accrue from earlier use of narrow-spectrum antibiotics, oral therapy, or avoidance, or discontinuation of antibiotics will be assessed in –
   (a) All patients in Groups 1, 2, and 3;
   (b) Patients with (i) influenza, (ii) RSV, and (iii) *S. pneumoniae* infection in Groups 1, 2, and 3,

8. Economic evaluation of near patient and rapid molecular diagnostic tests will be assessed by two main outcomes measures –
   (a) Cost per case detected,
   (b) Cost per QALY

Laboratory

9. Diagnostic accuracy,
   (a) Sensitivity,

(b) Specificity
(c) Positive predictive value,
(d) Negative predictive value
and discrepant analysis of near patient and molecular diagnostic tests, will be estimated in comparison with traditional and other (e.g., serology) laboratory tests.

10. Ease of use of rapid near patient and molecular tests
Molecular, near patient, and traditional laboratory culture diagnostic tests will scored independently for ease of use by three investigators.

11. Speed of tests, Will be assessed in terms of the median time from specimen collection to result:
(a) Appearing in the case-notes
(b) Appearing on Pathology Department results' database (APEX),
(c) Being phoned to the ward
(d) Being acted upon - in comparison to traditional laboratory culture.

Speed of tests will be determined for –
(i) All patients in Groups 1, 2, and 3;
(ii) Patients with influenza; RSV, and *S. pneumoniae* infection in Groups 1, 2, and 3,

Observational

12. Admission rates, for –
(a) Influenza,
(b) RSV, and
(c) S. pneumoniae
(d) **Anti-neuraminidase, anti-pneumolysin and 1gG antibody in sera and anti-pneumolysin and anti-neuraminidase induced CD4 T-cell activation and proliferation profiles from CD4 cells collected from peripheral blood.**

ANALYSIS

Sample size

The sample size is based on the admissions during 2002-03 and 2003-04 (September 1 – April 30) for elderly (≥65 years old) patients with acute cardio-pulmonary conditions, excluding angina and myocardial infarction. There were 2762 acute cardio-pulmonary admissions during September 1 – April 30 2002-03, and 2852 during 2003-04, i.e., an average of 11.57 admissions (≥65 years) per day.

The study will run for at 666 days (242 during each of Years 1 and 2, and 183 during Year 3), i.e., the number of eligible patients is estimated at 666x11.57=7705.6. We plan to recruit 5 days per week, which reduces the eligible number of patients to (5÷7)x7705.6=5504. We understand that two-thirds are admitted during the period 09:00-21:00h, which reduces the evaluable pool to 3669. We estimate that three-quarters of eligible subjects will participate, i.e., we expect to recruit 2752 elderly (≥65 years old) patients with acute cardio-pulmonary conditions. Of these, 664 are expected to have ICD codes for pneumonia; 556 are expected to have unspecified acute lower respiratory tract infections; 683 are expected to have exacerbations of chronic obstructive pulmonary disease; and 735 are expected to be admitted with heart failure.

We estimated the number of admissions in 'high-risk' 18-64 year-olds by extrapolation using (i) national cardio-pulmonary hospital admission data for patients aged 15-59 years, 60-74 years, and 75 years and older and (ii) the number of cardio-pulmonary admissions aged ≥65 years in Leicester.

We assumed that half of the patients admitted with pneumonia, unspecified lower respiratory tract infections, and exacerbations of COPD have underlying high-risk conditions. We expect to recruit 83 18-64-year old patients with pneumonia, 93 with unspecified lower respiratory tract infections, and 181 with COPD. These have not been included in the following estimates:

On the basis of historical data we expect that one-third of elderly patients with pneumonia have pneumococcal disease (i.e., 221) but expect the number identified by the pneumococcal antigen test to be higher. Of the 221, ~73 should be randomly allocated to the rapid near patient test (Binax NOW) (Group 1); the remainder will be randomised to the group tested by traditional methods (Groups 2 & 3). However, as identical sample sets will be taken from each individual, diagnostic accuracy will be assessed in a minimum of 221 subjects.

We expect that 10% of the 2752 (elderly) patients will have influenza A or B. Of the 275, one third (~91) will be allocated to Groups 1, 2, and 3. Identical sample sets will be taken from each individual, so the diagnostic accuracy of the tests will be assessed in all 275 subjects.

We expect that 5% of the 2752 (elderly) patients will have RSV A or B. Of the 137, one third (~45) will be allocated to the rapid molecular group (Group 2); the remainder (~90) will be allocated to the groups tested by traditional methods (Group 1 & 3). Identical sample sets will be taken from each individual, so the diagnostic accuracy of the tests will be assessed in all 137 subjects.

While the numbers of patients with influenza and RSV who are allocated to the 'rapid' near patient or molecular tests are comparatively small, the impact of a 'viral' infection (RSV or influenza) infection on patient isolation, antimicrobial prescribing, and clinical outcomes may be compared using larger combined groups – i.e., Rapid influenza & RSV (i.e., Quickview + molecular tests) n= (91 +91+45)=227 Traditional influenza & RSV n=(91+45+45)=182.

Statistical power:

This has been estimated for one laboratory and two clinical endpoints for the elderly population only.

Diagnostic accuracy
Assuming that the average sensitivity/specificity of the tests is 80%[90%] then allowing for a 20% dropout rate, a sample of 2752 (2000) i.e. only 2 winters) elderly (≥65 years) patients randomised into the trial would enable the sensitivity/specificity to be estimated to within, i.e. 2SE, 7.6% (8.9%) [5.7% (6.7%)] for a disease prevalence of 10%, and 5.4% (6.3%) [4.0% (4.7%)] for a disease prevalence of 5%.

Length of Stay
2752 patients would enable a Minimum Clinically Significant Difference (MCSD) [between diagnostic policies] of 1 day in the mean length of stay (assuming SD=6 days) to be detected at the 5% significance level with over 80% power, assuming a 20% dropout rate and adjusting for the fact that there are 3 groups.

Appropriate Isolation Levels: 2752 patients would also enable a Minimum Clinically Significant Difference (MCSD) [between diagnostic policies] of an improvement in appropriate use of isolation facilities from 5% to 15% to be detected at the 1% significance level with over 95% power, assuming a 20% dropout rate and adjusting for the fact that there are 3 groups.

Statistical methods:

All analyses for both process and clinical outcomes will be based on Intention to Treat (ITT) analyses.

Impact of test result on prescribing

The time to prescription of `narrow spectrum', `oral antibiotics' or `no antibiotics' between the three groups will be assessed using survival analysis techniques, whilst the use of neuraminidase inhibitors in those with influenza will be assessed using χ^2 tests, together with 95% CIs. Further analyses to allow for potential differences in patient demographics and baseline clinical characteristics between the three diagnostic test groups, and not allowed by stratification, will make use of Cox proportional hazards regression modelling in the case of time to appropriate prescribing and logistic regression techniques in the case of neuraminidase inhibitors.

Length of hospital stay

Length of hospital stay in the three diagnostic groups will initially be compared using non-parametric methods. Further analyses to allow for potential differences in patient demographics and baseline clinical characteristics between the three diagnostic test groups, and not allowed by stratification, will make use of generalised linear models in order to accommodate any skewness in the data.

Mortality rates

Mortality rates between the three diagnostic testing groups will be compared by means of a Log-Rank Test and Kaplan-Meier survival curves. Adjustment for potential differences in patient demographics and baseline clinical characteristics between the three diagnostic test groups, and not allowed by stratification, will make use of Cox proportional hazards regression methods.

Diagnostic accuracy

Sensitivity, specificity, positive predictive value of molecular and near patient diagnostic tests in comparison to traditional laboratory methods will be calculated together with 95% CIs. Heterogeneity in the sensitivity and specificity with respect to patient demographics and baseline clinical characteristics will be explored as secondary analyses using patient defined sub-groups.

Admission to Intensive Care

The proportions of patients in the three groups who are admitted to intensive care within the first 10 days of admission will be compared using χ^2 tests, together with 95% CIs. Further analyses to allow for potential differences in patient demographics and baseline clinical characteristics between the three diagnostic test groups, and not allowed by stratification, will make use of logistic regression techniques.

Ventilatory Support

The proportions of patients in the three groups who receive ventilatory support within the first 10 days of admission will be compared using χ^2 tests, together with 95% CIs. Further analyses to allow for potential differences in patient demographics and baseline clinical characteristics between the three diagnostic test groups, and not allowed by stratification, will make use of logistic regression techniques.

Appropriate Use of Isolation Facilities

In patients with confirmed influenza or RSV the time taken from admission to the MAU to admission to a single room (isolation cubicle) will be compared between the three diagnostic groups by means of a Log-Rank Test and Kaplan-Meier survival curves. Adjustment for potential differences in patient demographics and baseline clinical characteristics between the three diagnostic test groups, and not allowed by

stratification, will make use of Cox proportional hazards regression methods.

Quality of Life (EQ-5D)
Quality of life in the three diagnostic groups will initially be compared using non-parametric methods. Further analyses to allow for potential differences in patient demographics and baseline clinical characteristics between the three diagnostic test groups, and not allowed by stratification, will make use of generalised linear models in order to accommodate any skewness in the data.

Speed of Tests
Time taken to receive test results in the three diagnostic groups will initially be compared using non-parametric methods. Further analyses to allow for potential differences in patient demographics and baseline clinical characteristics between the three diagnostic test groups, and not allowed by stratification, will make use of generalised linear models in order to accommodate any skewness in the data.

Cost Data
Cost data will be analysed using parametric and non-parametric statistical methods which explicitly allow for the censoring of (indirect & total) costs at 28 days, i.e. for those patients who are not discharged from hospital within 28 days and thus enable an unbiased assessment of potential cost differences between the three diagnostic groups to be made. Estimation of the cost distribution over longer timescales will make use of extrapolation techniques using time of discharge obtained from hospital information systems.

TRIAL PLAN AND SCHEDULE OF ASSESSMENT

Assessments	Study Day **Admission** (Day 1)	**Days 2, 3, 4, 7 (±1), & 10 (±1)**	**Day 28** (±2)
Pre-study assessment by admitting medical team	✓		
Note time of admission (CRF)	✓		
Inclusion/Exclusion criteria check (CRF)	✓		
Written informed Consent (or Assent) (CRF)	✓	✓ (Consent upon recovery)	
Demography/immunisation status check (CRF)	✓		
Medical history/concomitant medications check (CRF)	✓		
Symptom assessment (CRF)	✓		
Clinical findings, including body weight and temperature (CRF). Establish when patient first becomes apyrexial ($\leq$37.2°C), requires supplemental O_2, and remains so for >24 hours (CRF)	✓	✓ (temperature, O_2)	
EuroQol. Quality of Life assessment (CRF) MRC Dyspnoea Scale Physical Activity Questionnaire	✓	✓	
Diagnostic studies ordered by the admitting medical team (CRF)	✓	✓	
Collection of trial specific diagnostic specimens (CRF): Nasopharyngeal (Quidel & virus culture) Nasopharyngeal Swabs Sputum (Gram stain & culture) Urine (Binax NOW) Blood (Blood cultures, serum antibodies)	✓	✓ (antibody, Day 10- 90) Day 2-3 if first swabs positive if available.	
Record time when diagnostic test results were made available to the ward nurses, and/or admitting team (CRF)	✓	✓	
Record antimicrobials & antivirals (identity,route, dose, time of administration) prescribed by admitting medical team (CRF)	✓		
Note the time of any changes in antimicrobials & antivirals (identity,route, dose, time of administration) prescribed by admitting medical team (CRF)		✓	
Bed location, i.e., record bay or a single room (CRF)	✓		
Note time of any subsequent change in isolation status (CRF)		✓	
ITU and ventilatory support: Document whether admitted or required ventilatory support (CRF)	✓	✓	
Date of hospital discharge/ Death within 28 days of admission (CRF)		✓	
Discharge diagnosis (CRF)		✓	

Note: Patients WILL NOT be re-recruited if readmission occurs during the 28-day follow-up

TABLE OF CONTENTS

1 BACKGROUND AND RATIONALE

1.1 Elderly demographics

Western industrialized nations face a population explosion among the elderly. In the UK the population aged ≥65 years, currently at ~12%, is projected to exceed the 1-14 years group by 2025 and surpass 20% overall by 2025. The number of people of state pension age is projected to increase by 10.2% between 2000 and 2011.[1] Preparation for this population growth, including the prevention and care of their illnesses is of paramount importance.

1.2 Acute respiratory illnesses

Illness surveys conducted in general practice indicate an overwhelming importance of acute respiratory illness in comparison to other conditions. During the most recent National Morbidity Study, a higher proportion of people (31%) consulted for respiratory conditions at least once during the year than for diseases in any other single ICD chapter. Overall, 67% of patients who saw their GP with a respiratory condition did so because of an acute infection, i.e., ~20% of all consultations in primary care occur because of acute respiratory infections, which are mostly viral. A similar picture has emerged in the United States. Some important age differences have emerged. There is a very high incidence of 'colds' and lower respiratory illness in the very young, whereas in the elderly, there is an age-related increase in morbidity and mortality from 'pneumonia and influenza.' We propose in this study to evaluate rapid diagnostic technologies for three target pathogens, influenza, respiratory syncytial virus, and *S. pneumoniae*, which are key aetiological agents of acute respiratory illness, and collectively are responsible for considerable morbidity and mortality in the elderly.

There have been no studies of the comparative incidence of influenza, RSV and pneumococcal disease among elderly cardiopulmonary admissions. Falsey *et al* [2] evaluated the number of hospitalisations of RSV infection relative to influenza in several thousand elderly people admitted to six hospitals in New York State between November and April 1989-1992. This and other studies suggest that RSV is likely to be found in ~5% of patients hospitalised with acute respiratory disease,[3-7] though with molecular diagnostic tests, the number identified is likely to be higher. Previous studies[2-4,6,7] indicate that at least 10% of cardiopulmonary admissions have influenza, but the number of admissions is influenced by the severity of epidemics, which have been mild since 1999/2000. None of these studies were conducted in the United Kingdom, and referral and admission practices may differ between countries. About one-third of all patients who are hospitalised in Northern Europe with community-acquired pneumonia have *S. pneumoniae* infection.[8]

1.3 Influenza

About 20% of children and 5% of adults worldwide develop symptomatic influenza A or B each year.[9] Although influenza A and B viruses circulate virtually every winter, quantification of the burden of influenza on consultations, emergency department examinations, hospital admissions, and mortality has been difficult because influenza lacks pathognomonic features, it co-circulates with other respiratory pathogens, and it causes a range of non-specific complications, such as exacerbations of chronic cardiopulmonary disease. During outbreaks, sentinel schemes, such as the Royal College of General Practitioners network in England, report increased consultation rates for influenza-like illness (ILI) and other respiratory syndromes that are

strongly associated with excess mortality. In England and Wales, an estimated 6,200 to 29,600 people died during each of the epidemics between 1975-76 and 1989-90.[10] These estimates are about ten times the number of death certifications for influenza, because the disease is the cause of many 'hidden deaths'. About 90% of these influenza-associated excess deaths are among people aged 65 years and older.[9] Although there are age-related increases in deaths from influenzal illness in both 'at-risk' and 'low-risk' groups,[11] most deaths and hospitalisations occur in elderly people with chronic cardiopulmonary disorders. The burden of influenza on winter admissions is poorly reflected by hospital activity analysis – as shown by our recent study of rapid molecular diagnosis of paediatric admissions in Leicester. We found that very few children with influenza were diagnosed or coded correctly.[12] Moreover, analysis of hospital activity statistics for Leicester for winters 2002/3 and 2003/4 revealed that only 2 of 5614 cardiopulmonary admissions among the elderly had a laboratory-confirmed diagnosis of influenza. We believe that this grossly underestimates the true burden of influenza in hospitals and reflects the views of hospital doctors that conventional diagnostic virology for respiratory pathogens is of no clinical value.

1.4 Respiratory syncytial virus

Respiratory syncytial virus (RSV) is a negative strand RNA virus belonging to the *Pneumovirus* genus of the *Paramyxoviridae* family. Respiratory syncytial virus (RSV) has a global distribution, causing sizeable outbreaks annually, usually between November – May. There are two antigenically distinct subtypes of RSV designated A and B; strain differences exist within each subgroup. Natural RSV infection produces incomplete protection and reinfection with RSV is common. Like influenza, RSV infection in the elderly has no pathognomonic features, and its distinction from other respiratory virus infections is impossible clinically. Evidence is accumulating that RSV is an important pathogen for the elderly, causing illness that is indistinguishable from influenza with upper respiratory symptoms that are frequently associated with lower respiratory tract involvement and pneumonia.[2,13,14] Outbreaks in residential care facilities are well documented and are of particular concern due to their high morbidity and mortality. Pneumonia occurs in 5% to 55% of cases, and mortality rates of up to 20% have been described.[2,13] Because RSV has traditionally been considered a paediatric infection, evidence of the virus in community-dwelling elderly, or admissions with cardiopulmonary disorders is usually not sought.

The lability of RSV; its brief period of shedding and low titre in nasal specimens during reinfection; the relative insensitivity of the complement fixation test (CFT), cell culture (even when performed under rigorous conditions including bedside inoculation) and rapid antigen detection tests (immunofluorescence and Directigen enzyme immunoassay) in the elderly; and the frequent co-circulation of RSV with influenza, may contribute to an underestimation of its incidence and burden.

Data from a prospective population-based study of upper respiratory tract infections in community dwelling elderly in Leicester, England demonstrated 3.6 RSV infections per 100 person years. Eighty-two percent (9 of 11) in the RSV subgroup had lower respiratory illness, 45% (5/11) were seen by a medical practitioner, and 36% (4/11) received antibiotics. A study of subjects with underlying chronic lung disease or congestive heart failure in Rochester, NY, reported an incidence of 4.3 RSV infections per 100 person winters. The clinical impact of RSV was considered significant as three of the eight RSV-infected subjects were

hospitalised. A more recent study by these investigators identified a rate of 3.7 RSV infections per 100 person winters in a healthy elderly population. Two of 12 RSV-infected elderly had complicated RSV illnesses (1 pneumonia on X-ray, 1 hospitalised), 5 (42%) required physician visits, and 4 (33%) received antibiotics.

1.5 Community-acquired pneumonia and S. pneumoniae

In adults, 60-80% of community-acquired pneumonia (CAP) cases are caused by bacteria;[15,16] rates of infection are highest in those aged $\geq$ 65 years. *S. pneumoniae* is the most common cause of bacterial pneumonia in adults and the elderly. The attack rate of CAP is influenced by the seasonal pattern of viruses predisposing to pneumonia.[16] In Leicester, weekly admissions data for the 1352 cases of CAP admitted during the winters of 2002/3 and 2003/4 shows two peaks of 5 and 6 weeks duration during 2002/3 and a 14-week peak during 2003/4, suggesting a possible relationship with respiratory virus activity. Between 9.5% - 48% of CAP may involve coinfection of typical and atypical organisms.[17] Of the 148 cases of *S. pneumoniae* identified by Porath *et al*,[18] 100 had co-pathogens identified, usually 'atypicals'. Although the clinical importance of polymicrobial infection is uncertain, mixed infection may be associated with a more complicated course.[19] The mortality from pneumococcal pneumonia in hospitals is ~2.5%.[8] Treatment cannot await the results of conventional microbiological tests, so an empiric regimen is necessary, which in the UK typically includes a β-lactam antibiotic, with or without a macrolide.[16]

It is possible that patients with a positive rapid pneumococcal antigen test result may receive a single antimicrobial agent, and that mortality of patients with polymicrobial infection including *S. pneumoniae* is increased. Oosterheert *et al*[20] recently undertook a systematic review to assess whether treatment with a β-lactam plus macrolide or quinolone monotherapy is truly superior to beta-lactam treatment alone. Eight relevant studies were selected. In six, significant reductions in mortality were found; in one, a reduction in hospital length of stay was found; and in another no beneficial effects could be demonstrated for treatment regimens with fluoroquinolone monotherapy or combinations of β -lactams and macrolides. The studies supporting the recommended treatment regimen were designed as non-experimental cohort studies. As a consequence, confounding may have influenced the results. In addition, the outcomes showed several inconsistencies. The authors concluded that a randomised controlled trial is warranted to circumvent the methodological flaws in the designs of the currently available studies, particularly as the addition of macrolides or treatment with fluoroquinolones may lead to enhanced antibiotic resistance, increased side effects, and healthcare-related costs. In Leicester, the recommended empiric therapy for patients hospitalised with CAP consists of monotherapy with a β-lactam agent or erythromycin if allergic to penicillin. Addition of a macrolide is not recommended unless the pneumonia is severe and therapy is adjusted 'as appropriate' at 48 hours if there has been no improvement. Although the available evidence does not indicate that rapid near patient pneumococcal antigen testing will adversely affect patient outcome, we plan that an independent Data Monitoring Committee conduct interim analyses to ensure that patient welfare is not adversely affected.

1.6 Diagnostic tests for influenza

Viral isolation and haemagglutination inhibition antibody testing are standard methods for influenza diagnosis, but have drawbacks. Virus isolation by culture from respiratory secretions may take a week or

more (a median of 8 days in one recent study);[21] it requires specialised laboratory facilities; and does not provide results that could influence the initiation of treatment. Serology provides a retrospective diagnosis. Neither test alone is considered a 'gold standard' for influenza diagnosis, since each lacks sensitivity, but culture and serology together have been used as 'gold standard' to assess molecular diagnosis.[22]

Tests for rapid diagnosis of influenza A and B virus by immunofluorescence of exfoliated nasopharyngeal cells have shown variable sensitivity (40 to 100%) and specificity (86 to 99%);[23] they require specialist equipment and expertise and are labour intensive. Rapid, near-patient tests for influenza vary in complexity, sensitivity, and specificity.[9] They can aid clinical management, but their value in the hospital setting in influencing prescribing and infection control is unclear. We plan to use the Quidel QuickVue influenza A and B test. It is the most rapid of the near patient tests; is particularly simple to perform; and has a median sensitivity and specificity of 80%.[9] Its diagnostic accuracy in the elderly is unknown. Molecular diagnosis of influenza by reverse transcription PCR (RT-PCR) provides improved sensitivity and specificity, allows accurate detection, and facilitates the subtyping of influenza.[24] Multiplex PCR has the added advantage of allowing identification of several infectious agents (e.g., influenza subtypes A/H1N1, A/H3N2, and B, and RSV types A and B) in one sample and in one reaction.[24,25] The technique is used routinely within the specialist diagnostic facilities of the Health Protection Agency, Colindale, where it has a sensitivity of 92% and specificity of 84%.[22] We plan to evaluate the ease of use and usefulness of PCR in Leicester as part of the process of distributing it more widely.

1.7 Diagnostic tests for RSV

Factors contributing to underestimations of the incidence and burden of RSV in the elderly include virus lability; the brief period of virus shedding and low titre of virus in nasal specimens during reinfection; the relative insensitivity of standard diagnostic tests – including the complement fixation test (CFT), virus culture (even when performed under rigorous conditions including bedside inoculation),[26] and rapid antigen detection tests (immunofluorescence and Directigen enzyme immunoassay) in the elderly;[26] and the frequent co-circulation of RSV with influenza.[10,12] Multiplex reverse-transcriptase polymerase chain reaction (RT-PCR) has emerged as a sensitive and specific method of detecting RSV infection.[25] Examination of nose and throat swabs by multiplex RT-PCR from 167 elderly subjects (age $\geq$65 years) who presented to their general medical practitioner with influenza-like illness during the winters 1995/6, 1996/7, and 1997/8 showed that 15% had RSV.[27] These investigators detected one RSV infection for every two influenza infections, suggesting that the previously unrecognised burden of RSV in the elderly may be substantial.

1.8 Diagnostic tests pneumococcal pneumonia

Diagnosis of pneumococcal pneumonia is complicated by the lack of a diagnostic reference standard that is highly sensitive and specific. Despite being the single most important pathogen causing CAP, *S pneumoniae* is undoubtedly underdiagnosed due to limitations of conventional tests. Limitations of Gram stain and culture of sputum include failure to obtain a sputum sample – only a minority of patients are able to produce sputum samples;[28] the overall diagnostic yield of sputum examination is very low (<25%);[28] and isolation of *S pneumoniae* from sputum may represent colonisation. Historically, blood cultures were considered a standard of care for the investigation of patients with CAP.[29] Positive blood culture results are found in <10%

of patients with CAP.[29,30] The test is rarely useful, as positivity becomes evident no earlier than 24h after obtaining the specimen, and results typically have little influence on therapeutic decisions and outcomes.[29,31-33] However, a review of patients with confirmed pneumococcal pneumonia, found that 42% of patients with positive blood culture results had their treatment changed as a result.[34] Since the overall prevalence of β-lactam resistance remains low in the UK, rapid near patient testing for pneumococcal infection could influence therapeutic decisions.

Measurement of pneumococcal antibodies has not proven reliable for diagnosing pneumococcal pneumonia.[35] PCR appears to be more sensitive than blood culture, but most studies have tested only a small number of samples, and have not compared different sample types from the same patients (see Murdoch *et al*).[36] Murdoch *et al*[36] used a nested PCR to target the pneumolysin gene in multiple sample types from 474 adults with CAP. The authors conclude that the pneumolysin PCR adds little to existing diagnostic tests and that it was less sensitive than the rapid urine antigen test. The detection of *S pneumoniae* antigens in the urine of patients with pneumonia has been extensively studied using a variety of techniques. While the performance of most tests has been disappointing, the Binax NOW urinary antigen test that we will use is simple to perform; it can detect the C polysaccharide cell wall antigen common to all *S pneumoniae strains*; and it provides results within 15 min. It has a sensitivity of 80% or more in adults and children, when positive blood cultures are used as the 'gold standard'.[37-41]

1.9 Clinical and cost-effectiveness of rapid diagnosis

Few studies have examined the impact of rapid diagnostic tests for influenza, RSV and *S. pneumoniae* on patient management, clinical outcomes, and cost-effectiveness. Potentially, the benefits might include: (i) improved infection control; (ii) more efficient use of antiviral therapy and (iii) more efficient use of antibiotics.

Several retrospective observational analyses have been done on the effectiveness of rapid tests for various respiratory virus infections in children.[42-44] Woo *et al* [42] observed a mean reduction in hospital stay of 1.3 days ($P<0.001$) following the introduction of rapid diagnosis. There were significant reductions in the duration of antibiotic use (52% reduction) and number of other microbiological investigations performed, and the cost of implementing the programme was more than offset by a reduction in the mean duration of stay. Barenfanger *et al*[43] found non-significant reductions in mortality and length of stay in the hospital following the introduction of rapid diagnosis. Byington *et al*[44] noted a significant decrease in inappropriate antibiotic use.

A retrospective observational study,[45] and a randomised controlled trial (RCT),[46] evaluated rapid near patient diagnostic tests for influenza in children's hospitals. The observational study showed that patients with a positive near-patient test were as likely to receive antibiotics as culture-confirmed cases, but the duration of antibiotic treatment was two days shorter. Patients with a positive diagnosis were also more likely to receive antiviral therapy ($p<0.001$). The RCT showed significant reductions in:- (i) investigations performed; (ii) antibiotics prescribed; (iii) use of antivirals, and (iv) the length of stay in the emergency department when the diagnosis of influenza was apparent at the time of assessment.

Cost-benefit analyses of near patient influenza testing have focused on its role in guiding treatment with neuraminidase inhibitors rather than the more efficient use of antibiotics or shorter duration of stay in hospitals.[47] No studies of the clinical and cost-effectiveness of rapid molecular testing for RSV have been carried out to our knowledge. Oosterheert *et al*[48] developed an algorithm to assess the potential costs and savings associated with the use of rapid diagnostic testing for pneumococcal pneumonia and evaluated the cost savings for 122 consecutively admitted patients with CAP. They identified no cost-reductions, which they ascribed to the small proportion of patients who could provide sputum, the small proportion of patients with CAP in their study who had pneumococcal pneumonia, and the small price difference between narrow-spectrum and broad spectrum therapy.

1.10 The EuroQol Instrument

The EuroQol instrument assesses quality of life by means of 5 questions with three possible answers to each question and produces valuations on a scale which has fixed points of 1 (full health) and 0 (death). It has been widely used in economic evaluations of health care interventions.[49,50] The EuroQol can be used to generate the outcome of 'Quality Adjusted Life Years' (QALYs) where quality of life in any health state is combined by the duration of that health state. Three different versions of the EuroQol instrument are available. These are a patient self-complete form, a form for completion by interview, and a proxy form (Appendix I).

1.11 Rationale for the study

Rapid near patient testing for influenza and pneumococcal infection, and rapid molecular tests for influenza and RSV will be justified if, as expected from existing knowledge, it can be shown that:

- Influenza, RSV, & *S. pneumoniae* infections occur as frequently as expected in the target population in the UK, & have an important impact on morbidity, mortality and quality of life.
- Rapid near patient and molecular tests are as reliably sensitive and specific in elderly patients admitted to a UK hospital as they are in other populations and settings; they are as easy to use as expected; and they provide clinically useful data to clinicians as rapidly as expected.
- Rapid diagnostic tests improve the opportunities for infection control in hospitals as expected by reliably identifying patients who, unless isolated, may transmit influenza or RSV to vulnerable patients and staff.
- Rapid diagnostic tests prevent or minimise unnecessary use of antibiotics in patients with viral infections.
- Rapid diagnostic tests aid therapeutic decisions in patients with CAP.
- Rapid diagnostic tests are not associated with increased morbidity or mortality in patients whose treatment would have been different without knowledge of the pathogen.

The selected study population is a key component of the recurrent bed crises experienced by the NHS in winter. Ironically, specific infective diagnoses are rarely obtained in these patients. This reflects the widespread perception that conventional test results are of dubious value, are usually available too late and that empirical therapy offers the best approach to management. As a result, very few centres have a clear view of the major pathogens responsible or have policies that take such information into account. Nonetheless, such information could and should have a profound influence on 1) antibiotic and antiviral use,

2) patient isolation and nursing policies, and 3) policies for immunisation of staff and the local community. Moreover, the timely provision of results through technologies to be assessed could transform attitudes to the value and applicability of results. Thus, while technology assessment is the primary driver and will be decisively achieved by our design, we contend that our proposal embodies exceptional added value by providing essential epidemiological data relating to a major burden on the NHS.

In this study, we will gather core information concerning the contribution of three key pathogens to winter admissions, validate rapid tests in two settings, and determine the effects of providing results on patient outcomes and management. We emphasize that, if the tests prove valid in this setting, our results will provide a major resource enabling improved planning in response to the winter burden of cardio-respiratory admissions in many different communities.

2 OBJECTIVES OF THE STUDY

2.1 Research objectives and *hypotheses*

In the Medical Admissions Units/Wards of the University Hospitals of Leicester, to:

1. Determine the diagnostic accuracy (sensitivity, specificity, positive and negative predictive values) of rapid molecular and near patient diagnostic tests for influenza, RSV and *S. pneumoniae* infections in comparison to traditional laboratory culture.

   The increased diagnostic accuracy of rapid molecular and near patient tests over traditional laboratory methods improves patient management through better use of antimicrobials and isolation facilities. Rapid molecular and near patient diagnostic tests for influenza, RSV and S. pneumoniae infections are more cost-effective than traditional laboratory diagnostic tests.

2. Assess the potential benefits of ease of use, and speed of rapid molecular and near patient diagnostic tests for influenza, RSV and *S. pneumoniae* infections, in comparison to traditional laboratory culture.

   Rapid molecular and near patient diagnostic tests for influenza, RSV and S. pneumoniae infections provide benefits in terms of (a) ease of use, and (b) more rapid results, in comparison to traditional laboratory culture.

3. Determine whether rapid molecular and near patient diagnostic tests for influenza, RSV and *S. pneumoniae* infections have any impact on prescribing.

   Rapid molecular and near patient diagnostic tests for influenza, RSV and S. pneumoniae infections result in earlier use of narrow-spectrum antimicrobial therapy;and/or an earlier switch from intravenous to oral therapy; and/or earlier discontinuation of antibiotics in patients infected with influenza and RSV - in comparison to traditional laboratory culture

4. Determine whether rapid molecular and near patient diagnostic tests for influenza, RSV and *S. pneumoniae* infections allow more appropriate use of isolation facilities, in comparison to traditional laboratory culture.

   Rapid detection of influenza and RSV by rapid molecular and near patient diagnostic tests leads to the appropriate isolation of patients, but only in hospitals/wards with an adequate provision of cubicles.

5. Compare the costs of performing rapid molecular and near patient diagnostic tests for influenza, RSV and *S. pneumoniae* infections, in comparison to traditional laboratory culture.

   The costs of performing rapid molecular and near patient diagnostic tests for influenza, RSV and S. pneumoniae infections, differ significantly from the cost of traditional laboratory culture.

6. Assess cost-savings associated with earlier use of narrow-spectrum antimicrobial therapy (or avoidance or discontinuation of antibiotics) in patients whose influenza, RSV and *S. pneumoniae* infections are diagnosed more rapidly by rapid molecular and near patient diagnostic tests, in comparison to traditional laboratory culture.

   The earlier use of narrow-spectrum antimicrobial therapy (or avoidance or discontinuation of antibiotics) in patients whose influenza, RSV and S. pneumoniae infections are diagnosed more rapidly by rapid molecular and near patient diagnostic tests results in significant cost-savings, in comparison to traditional laboratory culture.

7. Compare the outcome of patients whose influenza, RSV, and *S. pneumoniae* is diagnosed more rapidly by rapid molecular and near patient diagnostic tests, compared to those who are diagnosed by traditional laboratory culture.

   A streamlining of antimicrobial prescribing that may arise from more rapid diagnosis of influenza, RSV and S. pneumoniae infections by rapid molecular and near patient diagnostic tests does not adversely affect patient outcome.

8. Assess the impact that rapid molecular and near patient diagnostic tests have on the costs associated with an inpatient stay and on costs post-discharge up to a maximum of 28 days after admission.

   Any increase in costs incurred by rapid molecular and near patient diagnostic tests, in comparison to traditional laboratory culture, is more than offset by savings that arise from either rational antimicrobial prescribing or earlier discharge from the hospital.

9. To assess the impact that rapid molecular and near patient diagnostic tests have on quality-of-life, as measured by the EuroQol (Appendix I), and to use this information to estimate the quality adjusted life years (QALYs) generated during the 28 days after admission.

Rapid molecular and near patient diagnostic tests result in an improvement in quality-of-life, as measured by the EuroQol, which arises from streamlining of antibiotics and earlier discharge into the community.

10. To assess the cost-effectiveness of rapid molecular and near patient diagnostic tests in comparison to the cost/QALY of cases diagnosed correctly by traditional laboratory culture.To assess the cost-effectiveness of rapid molecular and near patient diagnostic tests in comparison to traditional laboratory culture. This will be done on the basis of both cost per case detected and cost per QALY.

    Rapid molecular and near patient diagnostic tests are more cost-effective than traditional laboratory culture.

11. **To explore whether patients with pneumococcal infection have lower levels of cellular and humoral immunity to the pneumococcus in comparison to patients who do not have pneumococcal infection.**

Patients with pneumococcal infection have lower levels of cellular and humoral immunity to the Pneumococcus in comparison to patients who do not have pneumococcal infection.

2.2 Observational objectives and hypotheses

In the Medical Admissions Units/Wards of the University Hospitals of Leicester, to:

11. Estimate the admission rates for influenza, RSV, and *S pneumoniae* in the target population.

    The admission rates in the target population are higher for S pneumoniae than influenza A and B. The admission rates for influenza A and B are similar to those for RSV A and B.

12. Compare the clinical characteristics and economic burden of influenza A and B and RSV A and B.

    The clinical characteristics and economic burden of influenza A and B and RSV A and B are similar.

13. Review the implications of rapid diagnosis on isolation policy, and review alternate approaches to managing the infection control issues.

    Rapid near patient and/or molecular diagnostic tests will reveal more cases of influenza and RSV who require isolation than can be isolated. Alternate approaches to managing the infection control issues, such as the use of influenza neuraminidase inhibitors, may be pertinent.

3 STUDY APPROVAL, CONSENT, ASSENT, AND PATIENT CONFIDENTIALITY

3.1 Declaration of Helsinki

This study will be conducted according to the 'Declaration of Helsinki' (as amended in Tokyo, Venice, Hong Kong, South Africa, 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000) (For Declaration of Helsinki, see Appendix II).

3.2 Ethics committee approval

This protocol and any accompanying material provided to the patient (such as patient information sheets or descriptions of the study used to obtain informed consent), will be submitted by the principal investigator to the Leicester Ethics Committee and to any other relevant Ethics Committee. Approval from the Committee must be obtained before starting the study, and should be documented in a letter to the investigator specifying the date on which the committee met and granted approval for the study and the protocol identification (title, version, date).

Any modifications made to the protocol after receipt of the Ethics Committee approval must be submitted by the investigator to the Committee in accordance with local procedures.

3.3 Patient informed consent/assent from a relative or carer

Patients who are capable of providing consent It is the responsibility of the clinical investigators or their deputies (Research Nurses/non-Consultant medical staff taking part in the study) to obtain signed informed consent from all prospective trial participants who are considered capable of providing consent (by the nursing and/or medical team providing clinical care). For such people signed informed consent will be obtained prior to entry to the study, after adequate explanation of the aims, methods, objectives, and potential hazards of the study, including any discomfort it may entail. Subjects will be given every opportunity to clarify any points they do not understand and if necessary ask for additional information. Prospective trial participants will be given time to reflect on their participation for a period not exceeding 8 hours of initial assessment by the admitting doctor on the Medical Admissions Unit, or another ward accepting acute medical admissions.

The clinical investigators or their deputies (Research Nurses/non-Consultant medical staff taking part in the study) must also explain to patients that they are completely free to refuse to enter the study or to withdraw from it at any time for any reason, without incurring any penalty or loss of any benefit to which they are otherwise entitled. Appropriate forms for documenting written informed consent will be provided by the Principal Investigator. Signed informed consent forms must be kept on file by the investigators in the Study Coordinating Centre (Infectious Diseases Laboratory, Leicester Royal Infirmary) and the collection of informed consent must be documented in the case report form. The clinical investigator, or his/her designee (Research Nurses/Research Doctor taking part in the study) must document in the case report form that informed consent was obtained BEFORE any trial specific procedures are performed on the subject.

Patients who are incapable of providing consent The Study Nurses or medical staff taking part in the study may additionally approach an accompanying relative, or a carer, of patients who can not give signed informed consent either because: (a) they are so breathless or confused that they are temporally unable to assimilate information regarding the study to judge whether to participate; or (b) the patient has pre-senile or senile dementia. In such cases, the study nurse or study doctor will seek informed Assent from either the patient's relative or a carer. The clinical investigators or their deputies must also explain to relatives or carer that they are completely free to refuse assent to enter the study or to withdraw it at any time for any reason, without incurring any penalty or loss of any benefit to which the patient is otherwise entitled. Appropriate forms for

documenting signed informed assent will be provided by the Principal Investigator. The clinical investigator, or his/her designee must document in the case report form that assent was obtained BEFORE any trial specific procedures are performed on the subject. The study nurse or study doctor will subsequently approach patients whose recovery enables them to provide signed informed consent.

3.4 Indemnity

- This is not a treatment study, rather it is a study of the impact of rapid diagnostic testing for influenza, respiratory syncytial virus, and *Streptococcus pneumoniae* infection on the management of acute cardio-pulmonary admissions in the elderly, and 18-64 year olds with chronic heart and lung conditions or pneumonia / influenza type symptoms. The investigations and monitoring that form part of this study are considered part of the normal care of adults meeting the case definitions. The Investigators and Study Nurses undertaking the clinical study (i.e., who recruit and monitor the patients, or do near patient, rapid molecular and conventional diagnostic microbiological tests) either hold, or will hold (when appointed) appointments, or honorary appointments, with the University Hospitals of Leicester Trust. Thus the investigators and their staff will be indemnified by the University of Leicester Hospitals Trust.

3.5 Study risks and benefits

Anticipated benefit for trial participants

A potential benefit to participants is the earlier diagnosis of influenza, RSV, and *S. pneumoniae* infection, with treatment tailored accordingly. This may improve the patients' quality of life by:

1. Reducing adverse drug events associated with broad-spectrum antibiotics (such as nausea and vomiting, and pseudomembranous colitis),
2. Patients with influenza who are diagnosed rapidly may benefit from treatment with a neuraminidase inhibitor if the interval between symptom onset and diagnosis is $\leq$48 h. Benefits might also accrue in the elderly with influenzal pneumonia, even if treatment is administered beyond 48h, but this has not been evaluated by RCT and is a theoretical benefit, and
3. Participants may benefit additionally from an increased level of monitoring of their illness in comparison to the standard level of care, with subsequent earlier recognition of complications, should they occur, and early intervention.

*Indirect benefit*s

1. Patients and staff in the hospital will benefit from improved infection control arising from rational use of single rooms and isolation cubicles.
2. The appropriate prescribing of neuraminidase inhibitors in the hospital may lessen viral shedding and reduce the risk of nosocomial transmission of influenza to patients and staff.

Risks

No specific risks due to participation in this study are anticipated since it is a surveillance, rapid diagnosis, and natural history study – with rapid diagnostic techniques being carried out in most patients in comparison to standard diagnostic testing. This is not an intervention study, i.e., we are not testing a new treatment, which

may be better or worse than standard therapy in terms of efficacy or adverse drug events. However, it is conceivable that some patients who are identified as having *S. pneumoniae* infection by the near patient rapid diagnostic test may have polymicrobial infection and that they may be disadvantaged by any early streamlining of antimicrobial therapy, should it occur. It should be noted, however, that there are specific guidelines in Leicester for the clinical management of community acquired pneumonia, and that the Investigators will not influence the antimicrobial prescribing by the medical team caring for the patient.

No procedures, including the collection of acute and convalescent blood samples for serology, will be carried out that could not be regarded as part of the normal investigation/care of the patient. Occasionally, blood collection causes pain and bruising at the site from where blood was drawn. It may also cause light-headedness and, rarely, fainting or infection.

3.6 Confidentiality and data protection

The investigator must ensure that the subject's anonymity will be maintained. On all documents and specimens that are to be removed from the investigational sites (i.e., from the University of Leicester and University Hospitals of Leicester Trust premises or storage facilities), subjects must ONLY be identified by a Trial Identification Number, their date of birth, and initials – not by their names or clinic number. The investigator should keep a separate confidential enrolment log (Appendix III), which matches identifying codes with the subjects' names and addresses and hospital numbers.

Since the study is being sponsored by the NHS National Coordinating Centre for Health Technology Assessment (NCCHTA), the Case Report Form and its contents will be retained on University of Leicester and University Hospitals of Leicester Trust premises or storage facilities.

Patient information will be stored on a password protected computer case report form/database (on an NHS computer within a secure facility). Patients' data will be aggregated into a relational database and no individual patient will be identified during health economic analyses in the University or any other analyses. Paper details (Case Report Forms/Consent) will be kept in a locked NHS facility, with only the Study Nurses, Principal Investigator, & Senior Clinical Investigators (Drs Steiner and Stephenson) having access to the keys/key-code. Printouts of the computer records will be stored within a secure NHS facility for a period of 15 years for future scientific scrutiny.

4 STUDY DESIGN

4.1 Overall design

The study is a prospective, randomised controlled trial to evaluate the impact of rapid diagnostic testing for influenza, respiratory syncytial virus and *Streptococcus pneumoniae*, on the management and outcome of acute cardio-pulmonary admissions in the elderly (age $\geq$65 years), and 'high-risk' individuals (have underlying chronic heart or lung disease, including asthma) who are 18-64-years of age. Or Pneumonia / influenza type symptoms**.**

Patients who present to Medical Admissions' Units in Leicestershire with an acute exacerbation of chronic cardio-pulmonary illness of ≤168 hours (7 days) duration, OR an acute cardio-pulmonary illness of ≤7 days duration (including: pneumonia; 'influenza'/influenza-like illness; 'exacerbations of chronic obstructive pulmonary disease' (COPD); bronchitis; asthma; congestive heart failure; or cardiac arrhythmia), who satisfy the study inclusion and exclusion criteria (See Sections 5.2 and 5.3), and can be recruited to the study within a 16-hour period of initial assessment by a doctor on the Medical Admissions Unit or another ward accepting acute medical admissions, will be randomised to one of three groups:

Group 1: Rapid near patient diagnostic tests (influenza and pneumococcus),
Group 2: Rapid molecular tests (influenza & RSV), plus laboratory pneumococcal antigen testing, and
Group 3: Traditional 'laboratory culture' (influenza, RSV, and *S. pneumoniae*)]

All tests will eventually be done on all patients who enter the study, but patients in Groups 1 and 2 will only be provided with rapid test results relating to their randomisation group.

On Day 1 (Day of admission to hospital)
Potential trial participants will be identified by the nursing or medical on-call staffs who provide care on the Medical Admissions Units, or the clinical team providing care on other wards that accept acute medical admissions with cardio-pulmonary conditions. The Study Nurse or Study Doctor will identify whether the patient is able to provide signed informed consent, or whether a relative or carer should be approached for signed informed assent. . Signed informed Consent (by the patient) or Assent (by a relative or carer be obtained before any trial related assessments or procedures are done. Subjects will be screened for eligibility (Inclusion/ Exclusion criteria check) and recruited only if all criteria are satisfied.

Demographic data and information on possible risk factors, immunisation status, relevant medical history, medications, and the nature of the acute cardio-pulmonary illness and clinical findings will then be documented. A Quality of Life assessment will be assessed by the EuroQol and a MRC Dyspnoea scale will be completed. The study nurse will document the diagnostic studies (e.g., chest radiograph, ECG, full blood count, cardiac enzymes, PaO_2) that were carried out by the admitting medical team; the nature, route of administration, and timing of any antimicrobial and antiviral treatments prescribed and given to the patient; and whether the patient was admitted to a bay area of the ward, or a single room. The study nurse will collect trial specific diagnostic specimens, including a nasopharyngeal swab for near patient (influenza, Quidel) testing, molecular diagnostic testing (influenza and RSV); and routine virological culture (influenza and RSV); blood for culture (*S. pneumoniae*) and antibody tests (influenza haemagglutination inhibition); sputum for Gram stain and culture (*S. pneumoniae*); and urine for pneumococcal antigen testing (Binax NOW).

Follow-up: Days 2, 3, 4,5,6, 7,8,9, 10, and 28: Subjects will be reviewed on the ward, if still an in-patient and other sources of information will be consulted so that the following data can be recorded in the CRF:

Time when diagnostic results were made available The time (24 hr clock and date) during the patient's hospitalisation (or after death, if relevant) when the patient's nursing/medical staff were given the results of

the different microbiological tests for influenza, RSV, and *S. pneumoniae*, together with the results, will be documented

Treatment The nature (name, dose, frequency, and route of administration) of all antimicrobials given to all patients within 10 days of admission will be documented. Note will be made of when 'broad-spectrum' treatment is switched to 'narrow-spectrum treatment'; when intravenous antibiotics are switched to oral therapy; and when antibiotics are discontinued. The requirement for supplemental oxygen will also be documented.

Isolation status, admission to ITU, and ventilatory support A record will be kept of (i) the patient's isolation status during the first 7 days of admission, and whether the patient was admitted to an ITU and/or required ventilatory support (including ward-based CPAP) during the first 10 days of admission.

Pyrexia The time (24 hr clock and date) during the patient's first 10 days of hospitalisation (or until death, if relevant) when the patient first became apyrexial (temperature $\leq 37.2^{o}C$), and remained so for a period of >24 hours will be recorded.

Convalescent serology A convalescent blood sample will be collected for paired acute and convalescent serology for influenza and RSV at 10 -90days.

Diagnostic studies The nature and results of all diagnostic studies (e.g., chest radiograph, ECG, full blood count, cardiac enzymes, PaO_2) carried out by the medical team will be recorded.

EuroQol The health status of all patients will be assessed by the EuroQol on days 7 and 28. Where patients have been discharged the EuroQol will be assessed by telephone interview of the patient or by postal questionnaire or by proxy (Appendix I).

Humoral and cell-mediated immunity to the pneumococcus. **Patients whose antigen tests for the pneumococcus are positive and an equivalent number of people whose pneumococcal test is negative will be bled on one occasion only within 5 days of hospital admission, for tests of cellular and humoral immunity to the pneumococcus.**

Physical Activity Questionnaire will be completed on day 2 or 3.

Deaths Deaths that occur within a maximum 28 days of hospitalisation will be identified by the study nurse and recorded in the CRF. **[Note: the principal investigator MUST be notified by the study nurse of all deaths that occur within 28 days of admission and of the patient's study group].**

Duration of hospitalisation The duration of hospitalisation, until discharge or death, will be obtained from the hospital activity analysis (i.e., computerised records). It will not form part of the routine monitoring of patients by the study nurse**.**

Discharge diagnosis The patient's discharge diagnosis will be obtained from the hospital activity analysis (i.e., computerised records). It will not form part of the routine monitoring of patients by the study nurse.

Resource use after discharge General practitioner consultations, hospital follow-up and other resource implications (e.g., prescriptions) for the period from discharge until Day 28 will be captured by a postal questionnaire (Appendix I). Patients will receive a reminder telephone call on Day 28 to return the questionnaire by post.

5 STUDY POPULATION

5.1 Study setting

This study will be done in three hospitals (Leicester Royal Infirmary, Glenfield Hospital, and Leicester General Hospital) that provide acute medical care for the University Hospitals of Leicester (UHL) Trust, Principally in the Medical Assessment Units. The UHL Trust serves a population of approximately 1 million subjects of all ages. The University Hospitals of Leicester NHS Trust is the only facility within the county of Leicestershire providing inpatient emergency medical care to the inhabitants of Leicestershire (population ~ 1 million). The laboratory tests will be carried out in the Molecular Diagnostic Laboratory, and Public Health Laboratory, Leicester Royal Infirmary. The study will carried out during the 36-month period August 1 2005- July 31 2008. Patient enrolment will occur during: September 1 2005 to June 30 2006; September 1 2006 to June30 2007; & September 1 2007 to June 30 2008.

5.2 Inclusion criteria

Men or women must satisfy the following to qualify for enrolment:

- Able and willing to give written informed consent, OR a relative or carer is able and willing to give informed Assent, *OR in the event that Informed Consent or Informed Assent cannot be obtained from the patient or carer (either because: (a) the patient is so sick (breathless or confused) that he/she is temporally unable to assimilate information regarding the study to judge whether to participate; or (b) the patient has pre-senile or senile dementia) f the following are satisfied:*

    (i) The patient provides written informed consent after reading the synopsis of the Patient Information Leaflet (Appendix IVa). In such cases the patient must be asked to provide Informed Consent after perusal of the 'Full' Information Leaflet when he/she is sufficiently well to do so;

- Age ≥65 years, OR age ≥18-64 years with underlying chronic heart or lung disease including asthma, **or pneumonia / influenza type symptoms.**
- Have an ***acute exacerbation*** of chronic cardio-pulmonary illness of ≤168 hours (7 days) duration, OR an ***acute cardio-pulmonary illness*** or influenza-like illness of ≤7 days duration, including:
    - Pneumonia*,
    - Influenza/influenza-like illness*,
    - Exacerbations of chronic obstructive pulmonary disease (COPD)*,
    - Bronchitis*,
    - Asthma*,
    - Congestive heart failure*, Cardiac arrhythmia*.
- Can be recruited to the study within a 16-hour period of initial assessment by an on-call doctor on the Medical Admissions Unit, or another ward accepting acute medical admissions,

- Able and willing to adhere to the procedures stated in the protocol
- Patients should have access to a telephone.

*NOTE: these are provisional or suspected clinical diagnoses that have been made either by the referring general medical practitioner or by the admitting medical team in the differential diagnosis. In general, it is expected that participants will have at least one respiratory symptom and one systemic symptom, OR ≥2 respiratory symptoms from at least two of the following bullet points, including:

Respiratory symptoms:
- Sore throat and/or hoarseness
- Nasal symptoms (stuffiness, and/or runny nose, and/or thick nasal discharge, or sneezing)
- Cough (new or increased)
- Sputum (new or increased)
- Wheezing (new or increased)
- Difficulty breathing/shortness of breath (new or increased)
- Chest pain with breathing

Systemic symptoms:
- Feverishness/sweating
- Chills, shivers, or rigors
- Tiredness or fatigue
- Decrease or loss of appetite
- Headache
- Muscle or body aches
- Generally feel unwell

5.3 Exclusion criteria

Patients with any of the following will be excluded from study enrolment:

- Inclusion criteria not met
- Angina/suspected myocardial infarction
- Were recruited to this study within 28 days of the current admission
- Could not be recruited to the study within a 16-hour period of initial assessment by a doctor
- Enrolment in a study of antimicrobial therapy of the illness for which the patient has been admitted.

6 STUDY PROCEDURES

6.1 Entry to the study (Day 1)

Only patients who meet all of the inclusion and none of the exclusion criteria described in sections 5.2 and 5.3 will qualify to enter the study. The following procedures will be performed and recorded at baseline (Day 1):

6.1.1 Identification of potential trial participants

Male or female patients with an acute respiratory illness or exacerbation of chronic cardio-pulmonary illness of recent onset (≤7 days (168 hours)), who are thought eligible by the admitting team (nursing and/or on-call medical staff on the Medical Admissions Unit), will be considered by the Study Nurse (or a Study Doctor) for inclusion in the study.

6.1.2 Approach to potential trial participants

Potential research participants will only be approached by the Study Nurse or Study Doctor after they have been admitted and assessed by the nursing staff on the Medical Admissions Unit or another ward that admits patients with acute cardio-pulmonary conditions, normally after they have been clerked by the admitting doctor. The Study Nurse (or Study Doctor) may approach an accompanying relative or carer of a referred

patient who can not give signed informed consent either because: (a) he/she is so breathless or confused that he/she is temporally unable to assimilate information regarding the study to judge whether to participate; or (b) the patient has pre-senile or senile dementia. In such cases, the Study Nurse or Study Doctor will seek informed Assent from either the patient's relative or a carer. The Study Nurse or Study Doctor will subsequently approach patients whose recovery enables them to provide signed informed consent.

6.1.3 Recruitment

Patients who evidently satisfy the entry criteria will be asked by the Study Nurses or medical staff carrying out the study whether they would be willing to learn about it, with a view to taking part. An Information Sheet will be given to each patient (Appendix IV); Patients who are not known to be suffering from dementia but are too unwell to read the Information Sheet may be recruited to the study provided that they give signed informed consent after reading the **Synopsis** of the Patient Information Sheet (Appendix IVa). This possible event will be documented in the Case Report Form. The patient should be re-consented using the Patient Information Sheet (Appendix IV) when he/she is able to assimilate information regarding the study to judge whether to continue. If the patient recovers and withdraws his/her consent, then all laboratory specimens will be destroyed and the patient will be excluded from the study. A modified version of the Information Sheet (Appendix V) will be given an accompanying relative or carer of a referred patient who can not give signed informed consent either because: (a) he/she is so sick (breathless or confused) that he/she is temporally unable to assimilate information regarding the study to judge whether to participate; or (b) the patient has pre-senile or senile dementia). . Potential trial participants will be informed that their participation is entirely voluntary, and that their medical care will not be adversely affected in any way if they decide not to participate. Consent to participate in the study will be obtained either at the end of the discussion, or at some point up to 16 hours after initial assessment by the doctor on the Medical Admissions Unit when there has been a chance for the patient to reflect on all the relevant issues (Appendix VI). All prospective trial participants who are considered capable of providing signed informed consent by the nursing and/or medical team providing clinical care will be required to give written informed consent before any trial related assessments or procedures are conducted. The Study Nurse or Study Doctor will only seek informed Assent (Appendix VII) from either a relative or a carer for subjects who are considered unable to give written informed consent. All subjects will subsequently be screened for eligibility (Inclusion/Exclusion criteria check) and recruited only if all criteria are satisfied.

6.1.4 Written informed consent/assent

Consent or Assent will be required to before any trial related assessments or procedures are conducted. Consent or Assent will be sought following discussion with the nursing and/or medical team providing clinical care about the patient's status. Subjects will be screened for eligibility (Inclusion/ Exclusion criteria check) and recruited only if all criteria are satisfied.

A Study Nurse or Doctor (after appropriate training), will obtain written informed consent from all individuals who are capable of providing consent prior to entry to the study, after adequate explanation of the aims, methods, objectives, and potential hazards of the study, including any discomfort it may entail. Such individuals will be told that they are completely free to refuse to enter the study or to withdraw from it at any

time for any reason, without incurring any penalty or loss of any benefit to which they are otherwise entitled. This information will be supplemented with a Patient Information Sheet, which provides written information concerning the above (Appendix IV). The Patient Information Sheet will be given to the research participants to be kept for reference. Subjects will be given every opportunity to clarify any points they do not understand and if necessary ask for additional information. Signed informed consent to participate in the study will be recorded on a Consent Form (Appendix VI) either at the end of the discussion, or at some point to 16 hours after initial assessment by the doctor on the Medical Admissions Unit when there has been a chance for the patient to reflect on all the relevant issues. Signed Informed Consent Forms must be kept on file by the Investigators in the Study Coordinating Centre (Infectious Diseases Laboratory, Leicester Royal Infirmary) and the collection of informed consent and transfer of the document to the Coordinating Centre must be documented in the CRF. The clinical investigator, or his/her designee (Research Nurses/Research Doctor taking part in the study) must document in the case report form that informed consent was obtained BEFORE any trial specific procedures are performed on the subject.

Signed informed Assent (See Appendix VII) should be obtained from a relative or carer of any patient who is incapable of providing consent, either because: (a) he/she is so breathless or confused that he/she is temporally unable to assimilate information regarding the study to judge whether to participate; or (b) the patient has pre-senile or senile dementia. Relatives and carers should be given the same information about the study (Information Sheet, See Appendix V) and opportunities to clarify any points and time to reflect on participation as given to patients able to give consent. The clinical investigators or their deputies must also explain to relatives or carer that they are completely free to refuse assent to enter the study or to withdraw it at any time for any reason, without incurring any penalty or loss of any benefit to which the patient is otherwise entitled. Appropriate forms for documenting signed informed assent (Appendix VII) will be provided by the Principal Investigator. The clinical investigator, or his/her designee must document in the case report form that assent was obtained BEFORE any trial specific procedures are performed on the subject. The study nurse or study doctor will subsequently approach patients whose recovery enables them to provide signed informed consent.

6.1.5 Inclusion/exclusion criteria

Patients will be considered eligible provided they meet all Inclusion/Exclusion criteria (See Sections 5.2 and 5.3 on Pages 14 and 15). The CRF will be documented accordingly.

6.1.6 Demography/immunisation status

Demographic data including details of residential status, smoking habits, alcohol consumption, household contacts, immunisation status (influenza and pneumococcus during the previous 3 years), and hospital admissions during the period 1st September – 30th April of the previous winter will be recorded in the CRF.

6.1.7 Medical history/regular medications

Details of the patients' concurrent medical conditions and regular medications will be obtained from the patient, and/or the medical practitioner's referral letter, and/or the admission clerking, and/or hospital notes, and/or family member/or carer, and will be recorded in the CRF.

6.1.8 Presenting symptoms and the interval between their onset and admission

Details of the patient's current symptoms and symptoms that appeared during the 168 hours (7 days) before consultation will be recorded in the patient's CRF together with the medical practitioner's referral diagnosis. The date and time of admission to the Medical Admissions Unit will be recorded in the CRF.

NOTE: Patients should not have new symptoms of >168 hours duration.

6.1.9 Clinical findings

The Study Nurse will record pertinent clinical findings including blood pressure, pulse, jugular venous pressure, oedema, respiratory rate, breath sounds, oxygen saturation, and temperature in the CRF, by reference to the examination findings documented in the medical case notes. Details of body weight and height will also be obtained if possible, either on admission, or subsequently.

6.1.10 Quality of Life assessment

All patients will be assessed by the EuroQol (Appendix I) on admission, (by proxy if they are incapable of completing the self-administered questionnaire or providing a verbal response) and the findings entered into the CRF.

6.1.11 Investigations ordered by the admitting medical team

The study nurse will record in the CRF the diagnostic studies (e.g., full blood count, routine biochemistry, blood sugar, cardiac enzymes, d-dimers, chest radiograph, ECG, oxygen saturation, blood gases, urinalysis, antibody studies, blood, sputum, and urine cultures, viral culture, antigen tests, etc) that were carried out by the on-call medical admissions team.

6.1.12 Antimicrobial and antiviral treatments prescribed

The Study Nurse will record in the CRF the names, route of administration, dose, frequency, and time of first administration of any antimicrobial or antiviral treatment that is prescribed by the responsible medical team during the first 24 hours of admission. Since it is possible that the patient may be seen by the Study Nurse before medication has been prescribed, it is essential that the medication given to the patient is constantly reviewed by the Study Nurse (See Section 6.2.2).

6.1.13 Randomisation and Trial Identification Numbers

Patients in each centre will be randomly allocated, using computer generated randomisation codes stratified by centre, to one of three diagnostic study groups:

Group 1: Rapid near patient diagnostic tests (influenza and pneumococcus),
Group 2: Rapid molecular tests (influenza & RSV), plus laboratory pneumococcal antigen testing, and
Group 3: Traditional 'laboratory culture' (influenza, RSV, and *S. pneumoniae*)]

The randomisation code (i.e., whether in Group 1, 2, or 3) will be included in sequentially numbered study packs that will be stored at each hospital (Leicester Royal Infirmary, Glenfield Hospital, and Leicester General Hospital). The Packs will be labelled as follows:

1-0001, etc, (Leicester Royal Infirmary site One)

2-0001, etc, (Glenfield Hospital siteTwo)

3-0001, etc, (Leicester General Hospital site **T**hree) which correspond to the Trial Identification Numbers allocated to participants at each study site.

The randomisation codes will be generated by the Department of Health Sciences, University of Leicester. The randomisation code will not be known by the Study Nurse until after the patient has signed the Patient Informed Consent Form. Only then will the study pack containing details of randomisation be opened.

6.1.14 Specimen collection and handling, and completion of investigation request forms

The sequentially numbered study packs will contain details of the randomisation code (See 6.1.11). Identical samples will be taken from each person, but samples for Study Groups 1, 2, and 3 will be processed differently depending on the participant's diagnostic study group. The following samples will be collected, and the time when ALL specimens were collected will be recorded in the CRF:

1. BLOOD

A 20 ml blood sample will be collected from **all study participants** for:

(i) ***Blood cultures*** 10mls of blood will be drawn by peripheral venepuncture for blood cultures. Blood culture bottles are routinely available in the MAU and acute medical wards. The blood culture bottles and investigation request form will be labelled with the patient's details (i.e., name, hospital number, and date of birth) in the standard way, BUT in addition with the participant's unique trial code and Study Group. Inclusion of the participant's name on both the label and request form should eliminate any confusion that might arise from use of a trial code alone. This sample may be additional to any blood culture investigation done by the medical team caring for the patient, but will be processed in the same way. The Investigation Request Form will be labelled with 'HTA Respiratory Infection Study'. The blood culture bottles and request forms will transported to the Clinical Microbiology Department using the routine transport arrangements.

(ii) ***Blood for antibody studies*** A 10-ml blood sample will be collected. The bottle will be labelled with the participant's unique trial code, date of collection, patient initials, and date of birth only, i.e., not with the participant's name. The Investigation Request Form will be labelled with 'HTA Respiratory Infection Study'. This sample will be additional to any acute serum sample that is collected by the medical team caring for the patient, and it will be processed differently. The blood sample will be transported to the Clinical Microbiology Department using the routine transport arrangements.

2. NASOPHARYNGEAL SPECIMENS

One (1) nasal, and one (1) nose and throat swab sample will be collected from **all study participants**. (See Appendix VIII) The nasal swab can be found in the The Quidel QuickVue Influenza A+B test kit, which is included in the sequentially numbered study packs. Similarly, nose and throat swabs for collection of nasopharyngeal specimens will be found in the participant's study pack. They will be used as follows:

- **GROUP 1 ONLY**: The swab in the Quidel QuickVue Influenza A+B test kit will be used in ***one nostril only***, specifically to collect a nasal sample – for rapid near patient testing, in the MAU/ward, of participants in Group 1.

  Patients randomised to Group 1 will have near patient tests for influenza A and B antigen done by the study nurse in an area of the MAU/ward where clinical tests such as urinalysis are done routinely. The instructions for collecting the Quidel QuickVue nasal sample and doing all tests are provided in Appendix IX. On completion of the test the Study nurse will:

  (a) Record the test result in the CRF;
  (b) Inform the team (i.e., the responsible nurse and/or doctor) that is providing clinical care of the patient of the rapid near patient test result - (i) verbally; and (ii) by insertion of an adhesive label in the notes. The clinical team should be told that a negative test does not exclude infection with influenza A or B.
  (c) Document in the CRF the time that the team was informed, and who was told.

- **GROUPS 1, 2, and 3**: The nose and throat swabs for the molecular tests and traditional tissue culture studies (for influenza and RSV) will be used to swab the throat and *the opposite nostril* (i.e., ONE nostril only) to that used previously and placed in virus transport medium. The instructions for collecting the nose and throat sample are provided in Appendix VIII. The nose and throat sample will be collected from ALL study participants, specifically for:
  - Prompt, conventional viral culture (Groups 1, 2, and 3);
  - Prompt, rapid molecular testing for influenza A and B and RSV A and B (Group 2);
  - Deferred, molecular testing for influenza A and B and RSV A and B (Groups 1 and 3);
  - Deferred Quidel QuickVue test for influenza A and B (Groups 1 and 2)
  - Possible future tests for other respiratory pathogens of stored specimens, if tests for influenza, RSV, and *S. pneumoniae* are negative.

  All tests will be done on samples collected from the participant's nose and throat using the swabs provided in individual patient Study Packs. The throat swab will be collected by vigorously rubbing the tonsils, soft palate, and back wall of the lower pharynx with the dry swab provided. The second nasal swab specimen should be collected from the participant's other nostril, i.e., NOT the nostril swabbed previously for the Quidel QuickVue near patient influenza A and B test, using the procedure described in Appendix IX. The swab tips are agitated in screw-capped study vials containing Virus Transport Medium, and are then cut off, or broken off, into the medium. The vials containing the nasopharyngeal specimen will be labelled with the participant's details, including name, date of birth, hospital number, date of collection, AND the participant's unique trial code corresponding to the sequentially numbered study pack. The Investigation Request Form will be labelled with 'HTA Respiratory Infection Study'. The specimens will be transported to the laboratory using the UHL transport system. Nasopharyngeal swabs will be collected from in patients if their initial swabs are positive on day 2 or 3.

3. SPUTUM

When possible freshly expectorated sputum sample will be collected from **all study participants** into a sputum pot for:

(i) ***Gram stain*** Sputum pots are routinely available in the MAU and acute medical wards. The blood sputum pot and investigation request form will be labelled with the patient's name, hospital number, and date of birth in the standard way, and with the participant's unique trial code corresponding to the sequentially numbered study pack. This sample may be additional to any sputum sampling done by the medical team caring for the patient, and will be processed in the same way. The Investigation Request Form will be labelled with 'HTA Respiratory Infection Study'. The sputum and request forms will transported to the Microbiology Department (Public Health Laboratory) using the routine transport arrangements. The specimen will be processed using standard operating procedures

(ii) ***Sputum culture*** The specimen collected for Gram staining (see above) will be cultured using standard operating procedures following receipt by the Clinical Microbiology Department.

4. URINE

A freshly voided urine sample will be collected from **all study participants** into standard containers for:

- GROUP 1 ONLY: Near patient testing for pneumococcal antigen using the Binax NOW test by the Study Nurse on the MAU/Ward.
- GROUP 2 ONLY: Prompt testing in the laboratory for pneumococcal antigen using the Binax NOW test on fresh 20 ml concentrated urine.
- GROUP 3 ONLY: Deferred testing for pneumococcal antigen using the Binax NOW test on stored 20ml concentrated urine.

- **GROUP 1 ONLY**: Patients randomised to Group 1 will have near patient tests for pneumococcal antigen done by the study nurse in an area of the MAU/ward where urinalysis is done routinely. A description of the test kit and obstructions for doing the test is provided in Appendix X. On completion of the test the Study Nurse will:

  (a) Record the test result in the CRF;
  (b) Inform the team (i.e., the responsible nurse and/or doctor) that is providing clinical care of the patient of the rapid near patient test result - (i) verbally; and (ii) by insertion of an adhesive label in the notes. The clinical team should be told that a negative test does not exclude infection with with *S. pneumoniae*.
  (c) Document in the CRF the time that the team was informed, and who was told.

- **GROUPS 2 and 3:**

  A **20**ml urine sample will be labelled with the participant's details, including name, date of birth, hospital number, and date of collection, AND in addition with the participant's unique trial code corresponding to the sequentially numbered study pack. The Investigation Request Form will be

labelled with 'HTA Respiratory Infection Study'. The specimens will be transported to the laboratory using the UHL transport system.

6.1.15 Initial isolation status

The study nurse will record in the CRF the isolation status of the patient (i.e., whether nursed in an 'open' environment, or in a single cubicle) on the MAU/medical ward when the diagnostic samples are collected. The time of specimen collection – and thus a temporal record of isolation status – will be noted in the CRF.

6.1.16 Initial investigations/procedures ordered by the medical team

The study nurse will record in the CRF details of the initial diagnostic studies carried out by the medical and nursing team providing clinical care, including, for example, ward urinalysis, FBC, blood biochemistry, cardiac enzymes, D-dimers, cardiac enzymes, blood gases, radiography, blood cultures, sputum culture, etc.

6.2 Follow-up (Days 2, 3, 4,5,6 7,8,9,10, and 28)

6.2.1 Time when diagnostic results were made available (Days 2, 3, 4, 7, and 10)

The times when the relevant diagnostic test results (See below) were made available to the medical and nursing team providing clinical care will be recorded in the CRF by reference to the APEX Pathology Computerised records system, and/or records held by the Department of Microbiology and Molecular Diagnostic Laboratory. Thus the times that the following test results were available will be entered into the CRF, even if the patient is discharged or has died:

Group 1:	
Rapid tests:	Rapid near patient test for influenza A and B (Quidel QuickVue influenza A and B)
	Near patient pneumococcal antigen test (Binax NOW test)
Conventional tests:	Viral culture test results (influenza A and B, RSV)
	Sputum Gram stain result
	Sputum culture result
	Blood culture result
Group 2:	
Rapid tests:	Rapid molecular tests for influenza A and B and RSV A and B,
	Laboratory pneumococcal antigen test (Binax NOW test) using concentrated urine
Conventional tests:	Viral culture test results (influenza A and B, RSV)
	Sputum Gram stain result
	Sputum culture result
	Blood culture result
Group 3:	
Conventional tests:	Viral culture test results (influenza A and B, RSV)
	Sputum Gram stain result
	Sputum culture result
	Blood culture result

6.2.2 Monitoring antimicrobial and antiviral treatment (Days 2, 3, 4,5,6 7,8,9, 10, and 28), and other new drugs prescribed for this illness

1. The relationship between the results of diagnostic tests and antimicrobial therapy is a key measure. The study nurse will record the name(s), the time when first administered, the dose, frequency of administration, and route of delivery of all newly prescribed antimicrobials/antivirals in the CRF. Subsequent changes in dose, frequency of administration, and route of delivery must be documented, even when the same antimicrobial is prescribed. The number of days that each formulation was prescribed will be documented in the CRF by reference to the Prescription Chart.
2. The nature of antibiotic, i.e., whether 'narrow/targeted' or 'extended'-spectrum, will be entered subsequently in the CRF.
3. Resource use is a key measure in this study, so the name(s), dose, frequency, and route of administration of newly prescribed drugs (including routinely prescribed medication at a higher dose, such as insulin) and intravenous fluids will be recorded in the CRF, by reference to the Prescription Chart.
4. The name(s), dose, frequency, and route of administration of any newly prescribed antimicrobial drugs that are given to the patient on discharge will be recorded in the CRF by reference to the Prescription Chart.
5. Details of any antibiotics prescribed for this condition by the GP following discharge will be captured by a Questionnaire (Appendix I, see Pages 60 and 65). Patients will receive a reminder telephone call on Day 28 to return the Questionnaire by post.

6.2.3 Isolation status (Days 2, 3, 4,5,6 7)

The relationship between isolation status and the results of diagnostic results is a key measure. The isolation status of the patient at mid-day on each of **Days 2, 3, 4,5,6 and 7** will be recorded in the CRF. The reason for isolation will be documented, since patients may be isolated for reasons other than an acute respiratory infection – e.g., winter vomiting disease, MRSA, diarrhoeal illness.

6.2.4 Diagnostic tests, procedures, and other resource implications (Days 2, 3, 4, 7, 10, and 28)

The following resources used by study participants will be recorded in the CRF:

1. **Diagnostic tests/procedures** The number and type of all investigations and procedures that were carried out by the medical team, up to a maximum of 28 days (up to midnight of day 28) following admission, will be recorded in the CRF. This information will be obtained following discharge from hospital or death, by reference to APEX and examination of the case-notes and X-rays.

2. **Additional treatment/support** The participant may require additional treatment or support, for example from a medical or nurse specialist, physiotherapist, nutritionists, occupational therapy, etc. This will be identified by reference to the medical records on discharge and recorded in the CRF.

3. **Discharge medication** The name, dose, frequency, and duration of any newly prescribed discharge medication (i.e., additional to regular prescriptions) will be recorded in the CRF for discharges occurring within 28 days of admission, by reference to the discharge letter.

4. **Hospital follow-up** The nature of further investigations (e.g., Chest-X-ray) and hospital follow-up visits that occur within 28 days of admission will be recorded in the CRF. This information will be captured by a Questionnaire (Appendix I, see Pages 60 and 65).

5. **General practitioner consultations (Day 28)** The number of occasions that patients were seen by their GP or deputising doctor after discharge (up to 28 days following admission), and whether it occurred in the surgery, another medical centre, or in the patient's home will be recorded in the CRF. This information together with the nature of any treatment received will be captured by a Questionnaire (Appendix I, see Pages 60 and 65).

6.2.5 Pyrexia (Days 2, 3, 4, 7, 10)

The study nurse will monitor the temperature chart and record when the patient first became apyrexial (temperature $\leq$37.2^{o}C), and remained so for a period of at least 24 hours.

6.2.6 Supplemental oxygen and CPAP (Days 2, 3, 4, 7, 10)

The study nurse will record in the CRF whether the study participant required supplemental oxygen (and CPAP) during days 1-10 of admission, and when supplemental oxygen (and CPAP) was no longer necessary (i.e., not required for a period of at least 24 hours).

6.2.7 Admission to ICU and ventilatory support (Days 2, 3, 4, 7, 10)

The study nurse will document in the CRF whether the patient was admitted to an Intensive Care Unit (ICU) during the first **10 days** of admission and whether he/she required ventilatory support. The total duration of stay on the ICU will be documented in the CRF.

6.2.8 Blood sampling for humoral and cell-mediated immunity to the pneumococcus.

Patients whose pneumococcal antigen test is positive (groups 1&2), and an equivalent number of people with a negative antigen test, will have a 25ml blood sample collected on one occasion during the first 5 days of hospital admission for tests of humoral and cell-mediated immunity to the pneumococcus.

6.2.9 Quality of Life assessment (Days 7 and 28)

All patients will be assessed by the EuroQol (Appendix I) on Days 7 and 28, and the results recorded in the CRF. Patients who have been discharged will be assessed by post using a questionnaire, or by a simple telephone interview.

6.2.10 Hospital discharge (Duration of hospitalisation/discharge diagnosis)

The duration of hospitalisation (until discharge or death) and discharge diagnosis will be obtained from the hospital activity analysis (i.e., computerised records) and recorded in the CRF.

6.2.11 Deaths

Deaths that occur within a maximum **28 days** of hospitalisation will be recorded in the CRF. [Note: the principal investigator MUST be notified by the study nurse of all deaths that occur within 28 days of admission and of the patient's study group]. [Note; the letter informing the GP of their patient's participation in the study will ask the GP to inform the investigators by fax should the patient die following discharge within 28 days of hospitalisation].

6.2.12 Convalescent serology (Day 10-90)

A 10ml convalescent blood sample will be collected from survivors at **10-90** days. The serum will be saved for paired acute and convalescent serology for influenza and RSV. The blood sample will be labelled with the participant's details, including name, date of birth, hospital number, and date of collection, AND in addition with the participant's unique trial code corresponding to the sequentially numbered study pack. The blood sample will be transported to the laboratory using the UHL transport system.

7 DATA ANALYSIS

Data management and statistical analyses will be performed in the Department of Health Sciences, University of Leicester.

7.1 Expected number of cases

No studies of the occurrence of influenza, RSV, and *S. pneumoniae* infections in elderly and other high-risk adults presenting to Medical Admission Units with cardio-pulmonary conditions that employ sensitive diagnostics have been carried out. Indeed, it is the uncertainty of their burden – together with questions concerning the clinical and cost-effectiveness of rapid diagnostic tests for these infections that has prompted the proposed study.

We plan to carry out the study in the Medical Admission Units/medical wards of the three acute hospitals in Leicester, which provide acute medical care for approximately 1 million people of all ages. Of these, ~14% (i.e., 140 000) are $\geq$65 years of age.

On the basis of medical admission data for the period September 1 – 30 April, 2002/3 and 2003/4, (when there were 2762 cardiopulmonary admissions during 242 days and 2852 during 243 days respectively), we anticipate that the acute hospitals will receive a daily average of 11.6 cardiopulmonary admissions $\geq$65 years of age, excluding admissions for angina and myocardial infarction. The study will run **for 43** weeks each season during the winters 2005/6 and 2006/7, and for 26 weeks during the period 1st September 2007 to 1st March 2008, i.e over 242 days during the 2005/6 and 2006/7 winters, and for 182 days during winter 2007/8 (September 1 – March 1). During this period, we estimate that 7706 cardiopulmonary admissions aged $\geq$65 years will be eligible for the proposed study. [Note: should there be a delay in starting the project we will recruit patients for 34 weeks during 'winter' 2007/8].

We will recruit patients five days per week. Thus, during the period Monday through Friday, the pool of eligible elderly ($\geq$65 years) patients that could be recruited will be 5504 (5/7 x 7706). We understand that

two-thirds are admitted during the period 09:00-21:00h, which reduces the pool of eligible subjects to 3669 (2/3 x 5504). We estimate that three-quarters of those who are invited to participate will do so (we carried out a study of respiratory virus infections in children at the Leicester Royal Infirmary; the parents of 86% agreed to participate). On the basis of these observations, we estimate that 2752 (3/4 x 3669) eligible elderly people could be recruited. Thus we anticipate recruiting a similar number of elderly patients as in the study by Falsey *et al,*[2] which was carried out in Rochester and Syracuse hospitals over three winters.

On the basis of pneumonia admissions data for the elderly (≥65 years) for the period September 1 – 30 April, 2002/3 and 2003/4 (when 1354 case were admitted over 485 days), we expect that 664 of an expected 1859 pneumonia (J12.9-J18.9) admissions will be recruited. Similarly we expect to recruit 556 participants with unspecified acute lower respiratory tract infections (J22.X), 683 with chronic obstructive pulmonary disease, and 735 participants with 'heart failure'.

The number of high-risk patients aged 18-64 years has not been factored into the above estimates. We have not been able to obtain historical data on the number of admissions among 18-64-year-olds to UHL hospitals who have underlying 'high-risk' medical conditions. However, by examining recent national data for admissions for comparable age groups, and making assumptions about the proportion of patients who have underlying high-risk conditions, we estimate that an additional 83 cases of pneumonia, 93 cases of unspecified acute lower respiratory tract infections, and 181 cases of COPD could be recruited.

- Based on the above, we expect to recruit 747 participants with pneumonia, of whom at least one third (n=249) should have *S. pneumoniae* infection. Of these, ~83 should be randomly allocated to the rapid near patient test (Binax NOW); the remainder will be randomised to the group tested by traditional methods. Thus the speed of diagnosis, impact of early diagnosis on prescribing, clinical outcomes, and costs will be assessed in groups having an estimated 83 and 166 subjects. However, as identical sample sets will be taken from each participant, the diagnostic accuracy of the tests will be assessed in all 249 subjects. The number of cases of *S. pneumonaie* infection that are likely to be identified among the anticipated 649 (556 +93) participants with unspecified acute lower respiratory tract infections is unknown, but their occurrence will add to the pool of cases for studies of diagnostic accuracy.

- On the basis of the Rochester study,[2] we expect that 10% of the 2752 elderly (≥65 years) participants will have influenza A or B. Of the 275, one third (~92) will be allocated to the QuickView near patient influenza immunoassay; one third will be allocated to the rapid molecular group; the remainder will be allocated to the group tested by traditional methods. Identical sample sets will be taken from each individual, so the diagnostic accuracy of the tests will be assessed in all 275 subjects.

- Similarly, we expect that 5% of the 2752 elderly (≥65 years) participants will have RSV A or B. Of the 138, one third (~46) will be allocated to the rapid molecular group; the remainder (~92) will be allocated to the group tested by traditional methods. We expect that very few of these will be found

positive by the routine tests employed. Identical sample sets will be taken from each individual, so the diagnostic accuracy of the tests will be assessed in all 138 subjects.

- While the numbers of patients with influenza and RSV who are allocated to the 'rapid' near patient or molecular tests are comparatively small (~92 + ~46 per elderly group, plus cases occurring in the 18-64-year-olds), the impact of a 'viral' infection (RSV or influenza) infection on patient isolation, antimicrobial prescribing, and clinical outcomes may be compared using a larger combined group – i.e.,

  Elderly

  Rapid influenza & RSV (i.e., Quickview + molecular tests) n= (92 + 92 + 46) = 230

  Traditional influenza & RSV n= (92 + 46 +46) = 184

  18-64 year-olds with high-risk conditions

  We estimate the total number of admissions in this group to be ~386, with 10% having influenza (n=~38), and 5% having RSV (n=~19)

  Rapid influenza & RSV (i.e., Quickview + molecular tests) n= (12 + 12 + 6) = 30

  Traditional influenza & RSV n= (12 + 6 +6) = 24

7.2 Background demographics

Demographic assessments including age, sex, ethnicity and other baseline characteristics (height, weight, smoking habits, alcohol consumption, 'high risk' chronic medical conditions, immunisation status, household size and makeup, contact with children, number of hospital admissions during the previous winter) for the whole study population will be summarised and tabulated. ***'High risk'*** heart and lung conditions are defined as follows :-

Those with chronic respiratory disease, including asthma	This includes chronic obstructive pulmonary disease (COPD, including chronic bronchitis and emphysema, bronchiectasis, cystic fibrosis, interstitial lung fibrosis, pneumoconiosis, asthma requiring continuous or repeated use of inhaled or systemic steroids or with previous exacerbations requiring hospital admission
Those with chronic heart disease	This includes chronic ischaemic heart disease, congenital heart disease and hypertensive heart disease requiring regular medication and follow-up (but excluding uncomplicated controlled hypertension), and chronic heart failure.

7.3 Definitions of influenza, RSV and S. pneumoniae positivity

Influenza positive Patients will be considered influenza positive if:

- The Quidel QuickVue Influenza A and B test is positive, and/or
- The multiplex PCR is positive, and/or
- Viral culture is positive, and/or
- Serology results indicate influenza infection (e.g., 4-fold increase in influenza A H3N2, H1N1, or influenza B HI antibody from acute to convalescent sera).

RSV positive Patients will be considered RSV positive if:

- The multiplex PCR is positive, and/or

- Viral culture is positive, and/or
- Serology results indicate RSV infection (e.g., ≥4-fold increase in RSV antibodies from Day 1 to Day 30).

***S. pneumoniae* positive** Patients will be considered influenza positive if:

- The Binax NOW *S. pneumoniae* antigen test is positive, and/or
- Blood culture is positive, and/or
- Sputum culture is positive, AND the sputum sample is macroscopically purulent, AND the sputum sample reveals increased numbers of polymorphonuclear leucocytes, AND the Gram stain is positive, AND there is moderate-to-high amounts of growth, according to criteria used by the laboratory.

Evaluations will be based on: (i) populations whose cardio-pulmonary illness is confirmed as due to influenza, RSV or *S. pneumoniae,* and (ii) the study groups comprising all people who are investigated by the different strategies under investigation (rapid near patient tests, *versus* rapid molecular diagnosis, *versus* conventional laboratory tests).

7.4 Statistical power

Statistical power has been estimated for one laboratory and two clinical endpoints for the elderly population only.

1. Diagnostic accuracy

   Assuming that the average sensitivity/specificity of the tests is 80%[90%] then allowing for a 20% dropout rate, a sample of 2752 (2000 i.e. only 2 winters) elderly patients randomised into the trial would enable the sensitivity/specificity to be estimated to within, i.e. 2SE, 7.6% (8.9%) [5.7% (6.7%)] for a disease prevalence of 10%, and 5.4% (6.3%) [4.0% (4.7%)] for a disease prevalence of 5%.

2. Length of Stay

   2752 patients would enable a Minimum Clinically Significant Difference (MCSD) [between diagnostic policies] of 1 day in the mean length of stay (assuming SD=6 days) to be detected at the 5% significance level with over 80% power, assuming a 20% dropout rate and adjusting for the fact that there are 3 groups.

3. Appropriate Isolation Levels:

   2752 patients would also enable a Minimum Clinically Significant Difference (MCSD) [between diagnostic policies] of an improvement in appropriate use of isolation facilities from 5% to 15% to be detected at the 1% significance level with over 95% power, assuming a 20% dropout rate and adjusting for the fact that there are 3 groups.

7.5 Endpoints

Endpoints are divided into clinical, financial, laboratory, and observational.

7.5.1 Clinical endpoints

1. Impact of test result on prescribing, specifically:-

   (a) Time, from admission to MAU, to first administration of 'narrow-spectrum' antibiotics, for patients in Groups 1, 2, and 3, who are prescribed antibiotics.

   (b) Time, from admission to MAU, to first administration of oral antibiotics, for patients in Groups 1, 2, and 3, who are prescribed antibiotics

   (c) Time (hours) from admission to MAU to prescription of 'no antibiotics' (oral or intravenous) administered to patients in Groups 1, 2, and 3, who have influenza or RSV.

   (d) Proportion of patients with influenza in Groups 1, 2, and 3 who are prescribed neuraminidase inhibitors.

2. Clinical outcomes, specifically:-

   (a) *Length of hospital stay* until discharge:
   First, for all patients in Groups 1, 2, and 3.
   Second, for all patients with (i) influenza; (ii) RSV; and (iii) *S. pneumoniae* infection in Groups 1, 2, and 3.

   (b) *Fever duration* (during the first 10 days of hospitalisation) Time from admission (hours) until the patient first became apyrexial (temperature $\leq 37.2^{o}C$), and remained so for a period of at least 24 hours:
   First, in all patients in Groups 1, and 2 in comparison to Group 3.
   Second, in patients with *S. pneumoniae* in Groups 1, and 2, in comparison to Group 3.

   (c) *Supplemental oxygen dependence and CPAP dependence* (during the first 10 days of hospitalisation) Times from admission (hours) until the patient required (i) no supplemental oxygen, and (ii) no CPAP, for a period of at least 24 hours:
   First, in all patients in Groups 1, and 2 in comparison to Group 3.
   Second, in patients with *S. pneumoniae* in Groups 1, and 2, in comparison to Group 3.

   (d) *Admissions to Intensive Care* (during the first 10 days of hospitalisation):
   First, the proportion of patients with *S. pneumoniae* infection in Groups 1, 2, and 3.
   Second, to better define the burden of influenza and RSV, the proportion of all patients with (i) influenza, and (ii) RSV who require ITU support.

   (e) *Ventilatory support* (during the first 10 days of hospitalisation):
   First, the proportion of patients with *S. pneumoniae* infection in Groups 1, 2, and 3.
   Second, to better define the burden of influenza and RSV, the proportion of all patients with (i) influenza and (ii) RSV who require ventilatory support.

   (f) *Deaths* (within 28 days of hospitalisation):
   First, the proportion of patients with *S. pneumoniae* infection in Groups 1, 2, and 3.
   Second, to better define the burden of influenza and RSV, the proportion of all patients with (i) influenza, and (ii) RSV, who die.

3. Quality of life, as measured by EuroQol, and quality adjusted life years generated during the 28 days after admission, will be assessed:

   (a) In all patients in Groups 1, and 2 in comparison to Group 3.

(b) Second, in patients in patients with (i) influenza, (ii) RSV, and (iii) *S. pneumoniae* in Groups 1, and 2, in comparison to Group 3.

4. Use of isolation facilities

(a) The time from admission to the MAU to the time of admission to a single room (isolation cubicle) will be compared for patients with confirmed influenza or RSV in Groups 1, 2, and 3.

(b) The proportion of patients with influenza or RSV in Groups 1, 2, and 3 who are isolated at any stage during the first 120 hours of the admission.

(c) The proportion of patients with *S. pneumoniae* infection in Groups 1, 2, and 3 who are inappropriately isolated for >12 hours.

7.5.2 Financial endpoints

1. Costs of diagnostic tests, Costs will be identified for:

(a) Rapid near patient test for influenza (Quidel);

(b) Rapid near patient test for pneumococcus (Binax NOW),

(c) Molecular (multiplex PCR) tests for influenza A and B and RSV A and B

(d) 'Prompt' antigen detection test for pneumococcus (Binax NOW), using x25 concentrated urine in the laboratory

(e) Culture (blood and sputum) for *S. pneumoniae*

(f) Gram staining of sputum samples

(g) Cell culture for influenza A and B

(h) Cell culture for RSV A and B

(i) Other tests that may be applied, eg immunofluorescence

2. Care costs Cost of inpatient stay (± 95%CI) will be determined for:

(a) All patients in Groups 1, 2, and 3;

(b) All patients (in all groups) with (i) influenza, (ii) RSV, and (iii) *S. pneumoniae* infection, and

(c) Patients with (i) influenza, (ii) RSV, and (iii) *S. pneumoniae* infection in Groups 1, 2, and 3.

For patients who are discharged within 28 days of admission, health care resource use in the period after discharge will be recorded using a simple questionnaire administered in a telephone interview.

3. Cost-savings that accrue from earlier use of narrow-spectrum antibiotics, oral therapy, or avoidance, or discontinuation of antibiotics will be assessed in –

(a) All patients in Groups 1, 2, and 3;

(b) Patients with (i) influenza, (ii) RSV, and (iii) *S. pneumoniae* infection in Groups 1, 2, and 3,

4. Economic evaluation of near patient and rapid molecular diagnostic tests will be assessed by two main outcomes measures –

(a) Cost per case detected,

(b) Cost per QALY

7.5.3 Endpoints for laboratory assessment of diagnostic tests

1. Diagnostic accuracy,

(a) Sensitivity,

(b) Specificity

(c) Positive predictive value,

(d) Negative predictive value, and

(e) Discrepant analysis of near patient and molecular diagnostic tests,

will be estimated in comparison with traditional and other (e.g., serology) laboratory tests.

2. Ease of use of rapid near patient and molecular tests

Molecular, near patient, and traditional laboratory culture diagnostic tests will scored independently for ease of use by three investigators, in terms of whether they can be done:

(a) On site,

(b) Require special laboratory facilities,

(c) Require special equipment,

(d) The number of reagents required,

(e) The number of steps and total benchtime,

(f) Ease of disposal/decontamination of used equipment and reagents,

(g) Technical competency required of the operator,

(h) Training period required to reliably carry out the test, and any

(i) Health and safety implications

3. Speed of tests,

Will be assessed in terms of the median time from specimen collection to result:

(a) Appearing in the case-notes

(b) Appearing on Pathology Department results' database (APEX),

(c) Being phoned to the ward

(d) Being acted upon - in comparison to traditional laboratory culture.

Speed of tests will be determined for –

(i) All patients in Groups 1, 2, and 3;

(ii) Patients with influenza; RSV, and *S. pneumoniae* infection in Groups 1, 2, and 3,

(iii) **Pneumococcal immnunity: Levels of anti-pneumolysin, anti-neuraminidase, and 1gG antibody in sera and anti-neuraminidase induced CD4 T cell activation and proliferation profiles from CD4 cells collected from peripheral blood will be compared in subjects with and without pneumococcal infection.**

7.5.4 Observational endpoints

1. Admission rates, for –

(a) Influenza,

(b) RSV, and

(c) *S. pneumoniae*

7.6 Statistical analysis

All analyses for both process and clinical outcomes will be based on Intention to Treat (ITT) analyses.

Impact of test result on prescribing The time to prescription of `narrow spectrum', `oral antibiotics' or `no antibiotics' between the three groups will be assessed using survival analysis techniques, whilst the use of neuraminidase inhibitors in those with influenza will be assessed using χ^2 tests, together with 95% CIs. Further analyses to allow for potential differences in patient demographics and baseline clinical characteristics between the three diagnostic test groups, and not allowed by stratification, will make use of cox proportional hazards regression modelling in the case of time to appropriate prescribing and logistic regression techniques in the case of neuraminidase inhibitors.

Length of hospital stay Length of hospital stay in the three diagnostic groups will initially be compared using non-parametric methods. Further analyses to allow for potential differences in patient demographics and baseline clinical characteristics between the three diagnostic test groups, and not allowed by stratification, will make use of generalised linear models in order to accommodate any skewness in the data.

Mortality rates Mortality rates between the three diagnostic testing groups will be compared by means of a Log-Rank Test and Kaplan-Meier survival curves. Adjustment for potential differences in patient demographics and baseline clinical characteristics between the three diagnostic test groups, and not allowed by stratification, will make use of Cox proportional hazards regression methods.

Diagnostic accuracy Sensitivity, specificity, positive predictive value of molecular and near patient diagnostic tests in comparison to traditional laboratory methods will be calculated together with 95% CIs. Heterogeneity in the sensitivity and specificity with respect to patient demographics and baseline clinical characteristics will be explored as secondary analyses using patient defined sub-groups.

Admission to intensive care The proportions of patients in the three groups who are admitted to intensive care within the first 10 days of admission will be compared using χ^2 tests, together with 95% CIs. Further analyses to allow for potential differences in patient demographics and baseline clinical characteristics between the three diagnostic test groups, and not allowed by stratification, will make use of logistic regression techniques.

Ventilatory support The proportions of patients in the three groups who receive ventilatory support within the first 10 days of admission will be compared using χ^2 tests, together with 95% CIs. Further analyses to allow for potential differences in patient demographics and baseline clinical characteristics between the three diagnostic test groups, and not allowed by stratification, will make use of logistic regression techniques.

Appropriate use of isolation facilities In patients with confirmed influenza or RSV the time taken from admission to the MAU to admission to a single room (isolation cubicle) will be compared between the three diagnostic groups by means of a Log-Rank Test and Kaplan-Meier survival curves. Adjustment for potential differences in patient demographics and baseline clinical

characteristics between the three diagnostic test groups, and not allowed by stratification, will make use of Cox proportional hazards regression methods.

Quality of Life (EQ-5D) Quality of life in the three diagnostic groups will initially be compared using non-parametric methods. Further analyses to allow for potential differences in patient demographics and baseline clinical characteristics between the three diagnostic test groups, and not allowed by stratification, will make use of generalised linear models in order to accommodate any skewness in the data.

Speed of Tests Time taken to receive test results in the three diagnostic groups will initially be compared using non-parametric methods. Further analyses to allow for potential differences in patient demographics and baseline clinical characteristics between the three diagnostic test groups, and not allowed by stratification, will make use of generalised linear models in order to accommodate any skewness in the data.

Cost Data

Cost data will be analysed using parametric and non-parametric statistical methods which explicitly allow for the censoring of (indirect & total) costs at 28 days, i.e. for those patients who are not discharged from hospital within 28 days, and thus allow an unbiased assessment of potential cost differences between the three diagnostic groups. Estimation of the cost distribution over longer timescales will make use of extrapolation techniques using time of discharge obtained from hospital information systems.

7.7 Data management

CRF data will be entered into a research system for collecting, managing, and reviewing clinical trial data. The data will be maintained on a secure server at the University Hospitals of Leicester. Statistical and health economic analyses will be done on anonymised data transferred from the UHL server to the Department of Health Sciences, University of Leicester. Throughout the study's life cycle, a history of users and corresponding access rights will be maintained and documented.

8 LABORATORY TESTS

8.1 Specimen collection

Instructions for the collection of specimens are outlined in detail elsewhere (See 6.1.14).

8.2 Specimen transport and processing

Instructions for the transport and processing of specimens are provided elsewhere (See 6.1.14).

9 SCHEDULING OF THE STUDY

Year 1: 1 June 2005 – 31 May 2006

1. **June – August 2005:** Purchase computers, refrigerators, & diagnostic kits and other consumables for first year; appoint three research nurses; post-doctoral RA; and MLSO; set up committees for

trial management and independent review & initiate work programme; generate randomisation code; produce and print CRF and develop trial database.

2. **July – August 2005:** Transfer of PCR Technology to Leicester; review SOP's in UHL Virology Laboratory.
3. **August 2005:** Pilot study of CRFs, patient recruitment, specimen handling, etc, and refinements as necessary.
4. **1 September 2005 – 30 June 2006:** Year 1 clinical trial; Trial Management Committee to review progress after 4 weeks of operation & continue with ongoing audit of patient recruitment, data entry into CRFs.
5. **December 2005 & March 2006:** Independent Data Monitoring Committee to hold their 1st & 2nd meetings and decide future meetings.
6. **Nov 2005, Jan 2006, Mar 2006, May 2006:** Review by Trial steering Committee of progress of Year 1 clinical trial.

Year 2: I June 2006 – 31 May 2007

1. **June – August 2006:** Carry out PCR, serology, & analysis of stored urine specimens; Audit and analysis of Year 1 data: purchase diagnostic kits and other consumables for second year. Prepare Year 1 analytical report.
2. **1 September - 14 December 2006:** Collate and analyse all diagnostic data from Year 1, including serological data; Prepare Year 1 analytical report by 14 December 2006.
3. **1 September 2006 – 30 June 2007:** Year 2 clinical trial; continue with ongoing audit of patient recruitment, data entry into CRFs.
4. **February – 31 May 2007** Carry out 'Ease of test' study during February-May.
5. **Nov 2006, Jan 2007, Mar 2007, May 2007:** Review by Trial steering Committee of progress of Year 1 and 2 data.

Year 3: I June 2007 – 31 May 2008

1. **Jun – July 2007:** Analyse data of 'Ease of test' and report findings
2. **May – Aug 2007:** Carry out PCR, serology, & analysis of stored urine specimens; Audit and analysis of Year 2 data: purchase diagnostic kits and other consumables for third year.
3. **June-Aug 2007:** Audit and analysis of Year 2 data: Determine the diagnostic accuracy of rapid molecular and near patient diagnostic tests; carry out PCR, serology, & analysis of stored urine specimens from year 2 study.
4. **1 Sept - 14 Dec 2007:** Collate and analyse all diagnostic data from Years 1 & 2, including serological data; prepare combined year 1 and year 2 analytical report by 14 December 2007.
5. **1st Sept 2007 to June 2008.:** Year 3 clinical trial; continue with ongoing audit of patient recruitment, data entry into CRFs.
6. **1 Jan – 31 Mar 2008:** Carry out PCR, serology, & analysis of stored urine specimens from year 2 study; collate all data in preparation for analyses.
7. **1 Apr – 31 May 2008:** Data analysis (Years 1-3 combined); preparation of draft 3-year report. Consider publication strategy.

10 INVESTIGATORS OBLIGATIONS

10.1 Data recording

The Principal Investigator is ultimately responsible for the quality of data recorded in the Case Report Form. These should be a complete and accurate record of the patients' data collected during the study.

10.2 Storage of study documentation

The documentation for this study should be stored securely, both in written and electronic formats. All data stored electronically should comply with the Data Protection Act. The investigator should arrange for retention of Case Report Forms, source records, and other supporting documentation for a minimum of 15 years.

10.3 Notification of primary care physician

It is the investigator's responsibility to notify primary care physicians of their patient's participation in the study, including its nature and duration, and expected benefits or possible adverse events. We will ask the primary care physician to notify the clinical investigators if a trial participant dies following discharge up to day 28 following admission. This will reduce the likelihood of the trialists contacting the patient or his/her carer for information post-mortem.

10.4 Reporting

The Principal Investigator MUST be notified as soon as possible (usually within 24 hours) by the study nurse of all deaths that occur within 28 days of admission and of the patient's study group. It is conceivable that early identification of *S. pneumoniae* infection by rapid near patient tests could result in streamlining of antibiotics from broad-spectrum to narrow spectrum antibiotics by the medical team caring for the patient, which could be detrimental if the patient had polymicrobial infection (i.e., infection with several pathogens).

The Principal Investigator, following discussion with members of the Trial Steering Committee, would inform the Chairman of the Independent Data Monitoring Committee (IDMC) of any concerns that patient welfare was being adversely affected by the study. The Principal Investigator would seek evidence of the following with each death: (i) Occurrence of polymicrobial infection; (ii) influence of rapid near patient tests on antibiotic prescribing for the deceased; and (iii) poor antimicrobial activity of the newly prescribed antibiotic against the causative pathogen(s), other than *S. pneumoniae*.

The Principal Investigator would immediately report to the Chairman of the Independent Data Monitoring Committee (IDMC) any evidence that patients whose *S. pneumoniae* infection was diagnosed by rapid tests had a worse outcome than those diagnosed by conventional tests, which could not have arisen by chance alone.

10.5 Protocol amendments

All amendments that have an impact on subject risk or the study objectives, or require revision of the informed consent document, must receive approval from the Ethical Committee prior to their implementation.

11 LIKELY OUTPUTS FROM THE STUDY

A substantial amount of information will be generated by the studies. Publications arising out of the work will focus on:

- ***Test parameters:*** The diagnostic accuracy (sensitivity, specificity, positive and negative predictive values) and discrepant analysis of molecular and near patient diagnostic tests, in comparison to traditional and other laboratory methods. The ease of use and speed of rapid, near patient; rapid molecular; and traditional laboratory tests for influenza, RSV, and *S. pneumoniae.*

- ***Clinical outcomes:*** Including the impact of rapid test results on antimicrobial prescribing, the appropriate use of isolation facilities; the length of hospital stay; admissions to Intensive Care; ventilatory support; deaths; and Quality-of-life, as measured by EuroQol, and quality adjusted life years (QALYs) generated during the 28 days after admission.

- ***Financial:*** The costs of diagnostic tests. Cost-savings associated with earlier use of narrow-spectrum antibiotics, oral therapy, or avoidance or discontinuation of antibiotics. Costs associated with inpatient stay and post-discharge, up to a maximum of 28 days after admission. Cost-effectiveness of rapid molecular and near patient diagnostic tests.

- ***Admission rates:*** for influenza, RSV, and *S pneumoniae* in the target population.

12 REFERENCES

1. Government Actuary's Department, National Population projections, 2000-base. Series PP2 No 23. London HMSO, 2002. Accessed at: http://www.statistics.gov.uk/downloads/theme_population/PP2No23.pdf
2. Falsey AR, Cunningham CK, Barker WH, *et al.* Respiratory syncytial virus and influenza A infections in the hospitalised elderly. *J Inf Dis* 1995;172:389-94.
3. Mufson MA, Chang V, Gill V, *et al.* The role of viruses, mycoplasmas and bacteria in acute pneumonia in civilian adults. *Am J Epidemiol* 1967;**86**:526-44.
4. Fransen H, Heigl Z, Wolontis S, *et al* Infections with viruses in patients hospitalised with acute respiratory illness. *Scand J Infect Dis* 1969;**1**:127-36.
5. Dowell SF, Anderson LJ, Gary HE, *et al.* Respiratory syncytial virus is an important cause of community-acquired lower respiratory infection among hospitalized adults. *J Inf Dis* 1996;**174**:456-62.
6. Glezen WP, Greenberg SB, Atmar RL, Piedra PA, Couch RB. Impact of respiratory virus infections on persons with chronic underlying conditions. *JAMA* 2000;**283**:499-505.
7. Falsey AR, Walsh EE, Hayden FG. Rhinovirus and coronavirus infection-associated hospitalizations among older adults. *J Infect Dis* 2002;**185**:1338-41.
8. Macfarlane J. The clinical impact of pneumococcal diasease. International Congress and Symposium Series, No. 210. Ed RT Mayon-White. Royal Society of Medicine Press, London, 1995, pp 9-17.
9. Nicholson KG, Wood JM, Zambon M. Influenza. *Lancet* 2003;**362**:1733-45.
10. Nicholson KG. Impact of influenza and respiratory syncytial virus on mortality in England and Wales from January 1975 to December 1990. *Epidemiol Infect* 1996;**116**:51-63.
11. Meier CR, Napalkov PN, Wegmüller Y, *et al.* Population-based study on incidence, risk factors, clinical complications and drug utilization associated with influenzas in the United Kingdom. *Eur J Clin Microbiol Infect Dis* 2000;**19**:834-42.
12. Nicholson KG, McNally T, Silverman M, *et al.* Influenza, respiratory syncytial virus and human metapneumovirus hospitalisations among young children: a prospective observational study (submitted for publication).

13. Nicholson KG, Baker DJ, Farquhar A, *et al*. Acute upper respiratory tract viral illness and influenza immunization in homes for the elderly. *Epidemiol Infect* 1990;**105**:609-18.
14. Nicholson KG, Kent J, Hammersley V, Cancio E. Acute viral infections of upper respiratory tract in elderly people living in the community: comparative, prospective, population based study of disease burden. *BMJ* 1997;**315**:456-62.
15. File TM. Community-acquired pneumonia. Lancet 2003;**362:**1991-2001.
16. Baldwin DR, Macfarlane JT, Community-acquired pneumonia. Ch 34. In: Infectious Diseases, 2nd edition, Eds: J Cohen, WG Powderly, Edinburgh, Mosby, 2004, Vol 1, pp369-80.
17. Campbell SG, Marrie TJ, Anstey R, *et al.* The contribution of blood cultures to the clinical management of adult patiernts admitted to the hospital with community-acquired pneumonia. A prospective observational study. *Chest* 2003;**123**:1142-50.
18. Porath A, Schlaeffer F, Pick N, et al. Pneumococcal community-acquired pneumonia in 148 hospitalized adult patients. *Eur J Clin Microbiol Infect Dis* 1997;**16**:863-70.
19. Kauppinen M, Saikku P, Kujala P, et al. Clinical picture of community-acquired Chlamydia pneumoniae requiring hospital treatment: a comparison between chlamydial and pneumococcal pneumonia. *Thorax* 1996;**51**:185-9.
20. Oosterheert JJ, Bonten MJ, Hak E, et al. How good is the evidence for the recommended empirical antimicrobial treatment of patients hospitalized because of community-acquired pneumonia? A systematic review. *J Antimicrob Chemother*. 2003;**52**:555-63.
21. Woo PCY, Chiu SS, Seto W-H, et al. Cost-effectiveness of rapid diagnosis of viral respiratory tract infections in pediatric patients. *J Clin Microbiol* 1997;**35**:1579-81.
22. Zambon MC, Hays J, Webster A, et al.. Diagnosiso finfluenza in the community. Relationship of clinical diagnosis to confirmed virological, sserologic, or molecular detection of influenzaa. *Arch Intern Med* 2001;**161**:2116-22.
23. Noyola DE, Clark B, O'Donnell FT, *et al.* comparison of a new neuraminidase detection assay with an enzyme immunoassay, immunofluoprescence, and culture for rapid detection of influenza a and b viruses in nasal wash specimens. *J Clin Microbiol* 2000;**38**:1161-5.
24. Ellis JS, Fleming DM, Zambon MC. Multiplex RT-PCR for surveillance of influenza in England 1995/1996. *J Clin Microbiol* 1997;**35**:2076–82.
25. Stockton J, Ellis JS, Saville M, Clewley JP, Zambon MC. Multiplex PCR for typing and subtyping influenza and respiratory syncytial viruses. *J Clin Microbiol* 1998;**36**:2990–95.
26. Falsey AR, McCann RM, Hall WJ, Criddle MM. Evaluation of four methods for the diagnosis of respiratory syncytial virus infection in older adults. J Am Geriatr Soc 1996;44:71-73.
27. Zambon MC, Stockton JD, Clewley JP, Fleming DM. Contribution of influenza and respiratory syncytial virus to community cases of influenza-like illness: an observational study. *Lancet* 2001;**358**:1410-16.
28. Ewig S, Schlochtermeier M, Goke N, et al. Applying sputum as a diagnostic tool in pneumonia. *Chest* 2002;**121**:1486-92.
29. Campbell SG, Marrie TJ, Anstey R, et al. The contribution of blood cultures to the clinical management of adult patients admitted to the hospital with community-acquired pneumonia. A prospective observational study. *Chest* 2003;**123**:1142-50.
30. Mandell LA, Marrie TJ, Grossman RF, et al. Canadian guidelines for the initial management of community-acquired pneumonia: an evidence based update by the Canadian Infectioous Diseases Society and the Canadian Thoracic Society. *Clin Infect Dis* 2000;**31**:383-421.
31. Moine P, Vercken J-B, Chevret C, et al. Severe community-acquired pneumonia: etiology, epidemiology and prognosis factors. *Chest* 1994;**105**:1487-95.
32. Chalasani NP, Valdecanaas MAL, Gopal AK, et al. Clinical utility of blood cultures in adult patients with community-acquired pneumonia without defined underlying risks. *Chest* 1995;**108**:932-8.
33. Sanyal S, Smith PR, Saha AC, et al. Initial microbiologic studies did not affect outcome in patients hospitalised with community-acquired pneumonia. *Am J Respir Crit Care Med* 1999;**160**:346-8.
34. Waterer GW, Jennings SG, Wunderink RG. The impact of blood cultures on antibiotic therapy in pneumococcal pneumonia. Chest 1999;116:1278-81.
35. Musher DM, Meddiwala MR, Phan HM, et al. Nonspecificity of assaying for IgG antibody to pneumilysin in circulating immune complexes as a means to diagnose pneumococcal pneumonia. *Clin Infect Dis* 2001;**32**:534-8.
36. Murdoch DR, Anderson TP, Beynon KA, et al. Evaluation of a PCR assay for detectionof Srteptococcus pneumoniae in respiratory and nonrespiratory samples from adults with community-acquired pneumonia. *J Clin Microbiol* 2003;**41**:63-6.
37. Murdoch DR, Laing RTR, Mills GD, et al. Evaluation of a rapid immunochromatographic test for detection of Streptococcus pneumoniae antigen in urine samples from adults with community-acquired pneumonia. *J Clin Microbiol* 2001;**39**:3495-8.
38. Farina C, Arosio M, Vailati F, et al. Urinary detection of Streptococcus pneumoniae antigen for diagnosis of pneumonia. *New Microbiol* 2002;**25**:259-63.
39. Smith MD, Derrington P, Evans R, et al. Rapid diagnosis of bacteremic pneumococcus infections in adults by using the Binax NOW Streptococcus pneumoniae urinary antigen test: a prospective controlled clinical evaluation. *J Clin Microbiol* 2003;**41**:2810-3.

40. Roson B, Fernandez-Sabe N, Carratala J, Verdaguer R, Dorca J, Manresa F, Gudiol F. Contribution of a urinary antigen assay (Binax NOW) to the early diagnosis of pneumococcal pneumonia. *Clin Infect Dis* 2004;**38**:222-6.
41. Dominguez J, Blanco S, Rodrigo C, et al. Usefulness of urinary antigen detection by ann immunochromatographic test for diagnosis of pneumococcal pneumonia in children. *J Clin Microbiol* 2003;**41**:2161-3.
42. Barenfanger J, Drake C, Leon N, *et al.* Clinical and financial benefits of rapid detection of respiratory viruses: an outcomes study. *J Clin Microbiol* 2000;**38**: 2824-8.
44. Byington CL, Castillo H, Gerber K, et al. The effect of rapid respiratory viral diagnostic testing on antibiotic use in a children's hospital. *Arch Pediatr Adolesc Med* 2002;**156**:1230-4.
45. Noyola DE, Demmler GJ. Effect of rapid diagnosis on management of influenza A infections. *Pediatr Infect Dis J* 2000;**19**:303-7.
46. Bonner AB, Monroe KW, Talley LI, et al. Impact of the rapid diagnosis of influenza on physician decision-making and patient management in the pediatric emergency department: results of a randomised, prospective, controlled trial. *Pediatrics* 2003;**112**:363-7.
47. Hueston WJ, Benich JJ. A cost-benefit analysis of testing for influenza A in high-risk adults. *Ann Fam Med* 2004;**2**:33-40
48. Oosterheert JJ, Bonten MJM, Buskens E, et al. Algorithm to deftermine cost-savings of targeting antimicrobial therapy based on results of rapid diagnostic testing. *J Clin Microbiol* 2003;**41**:4708-13.
49. The EuroQol Group. EuroQol – a new facility for the measurement of health-related quality of life. *Health Policy* 1990;**16**:199-208.
50. Brooks R. EuroQol: the current state of play. *Health Policy* 1996;**37(1)**:53-72.
51. Quach C, Newby D, Daoust G, et al. QuickVue influenza test for rapid deection of influenza A and B viruses in a pediatric population. Clin & Diag Lab Immunol 2002;9:925-6. 2002
52. Department of Health. NHS reference costs. Department of Health. March 2004. http://www.dh.gov.uk/
53. Netten J, Curtis J. Unit costs of health and social care. 2003. Canterbury, PSSRU, University of Kent.

APPENDIX 1

PROTOCOL FOR COLLECTION OF HEALTH ECONOMIC DATA

The EuroQol questionnaire for this study will be completed at baseline, 7 days and 28 days and the same procedure should be followed.

1. Before completing the EuroQol questionnaire at each time point the research nurse will complete the Quality of life assessment form.
2. There are four ways the EuroQol questionnaire can be completed:
    a. Subject is unconscious and is declared as such.
    b. Self-completion by the respondent.
    c. Interview by the research nurse for those for example who are visually impaired or for some other reason cannot self complete. At the 7 and 28-day time points, if they have been discharged, the research nurse will carry out a telephone interview.
    d. For those who cannot complete the questionnaire due to other circumstances, for example they are too ill or are cognitively impaired, a proxy should be identified (ideally somebody who is familiar with the subject).

    Those subjects who are either unconscious or have a proxy response at an early time point may become well enough to self-complete the EuroQol at either the 7day or 28 day time point. These subjects should then self-complete (or interview complete) the EuroQol.
3. If a proxy is being used then the research nurse should fill in the subjects name in the lines provided on pages 2 and 3 and the box on page 3.
4. Once the questionnaire as been completed the research nurse should ensure that all sections of the EuroQol have been completed (one answer in each section).
5. All completed questionnaires should be stored together with the subjects Quality of life assessment form.

7 and 28 day follow up questionnaires for those who have been discharged.

1. There is an additional questionnaire to be completed if the subject as been discharged.
2. If a proxy is to be used then the same proxy should be used to complete all questionnaires for the subject if possible.
3. The research nurse should obtain the proxy's address and post the questionnaire to them with a stamped addressed envelope before the 7 or 28-day time point.
4. At the 7 day time point the respondents should be sent the appropriate EuroQol (either self-complete or proxy). Those who require it should have a telephone interview (see point C above)
5. At 28 days all discharged subjects should be sent appropriate 28 day questionnaire (either self-complete or proxy). Again, those who would be unable to complete a questionnaire should have a telephone interview (see point C above).
6. Non-responders should be sent another form and reminder 7 days after this period.

EuroQol Assessment – Inpatient (Baseline, 7 and 28 days after admission)

REMINDER – ONLY TEXT IN ITALICS SHOULD BE READ OUT TO THE INTERVIEWEE. BOLD CAPITALS ARE INSTRUCTIONS TO THE INTERVIEWER. PLEASE FILL IN ALL RELEVANT SECTIONS. ANSWER YES/NO QUESTIONS BY CIRCLING APPROPRIATE NUMBER.

FILL IN RESPONDENT DETAILS BEFORE INTERVIEW

Patient Name: _____ Study Number: _____

Admission date: ____/____/____

Baseline EuroQol

Date of interview: ____/____/____

Interviewer Name: _____

Is patient unconscious?

Yes…….1 **DISCONTINUE INTERVIEW**

No……..2

IF PATIENT IS ABLE TO RESPOND TO INTERVIEWER SAY: *Hello. Thank you for agreeing to take part in this study. We are interested in how you feel today. To find this out we would like you to fill in a short questionnaire. Do you feel able to complete this questionnaire yourself?*

Is patient able to self-complete Euroqol?

Yes…….1 **GIVE PATIENT SELF COMPLETE EUROQOL AND ATTACH COMPLETED FORM TO BACK OF THIS FORM**

No……..2 **COMPLETE SECTION 2**

Section 2 EuroQol by interview

Is patient able to complete Euroqol by interview?

Yes…….1 **CARRY OUT EUROQOL INTERVIEW**

No……..2 **COMPLETE SECTION 3**

ASK *We will also be asking you to fill in a short questionnaire 1-month after you were admitted to hospital. Do you think you will be able to complete a postal questionnaire at this time or will you have someone who can help you with this?*

Yes…….1

No……..2

ASK *Can we carry out this interview by telephone?*

Yes…….1

No……..2

Section 3 EuroQol by Proxy
Can you identify a suitable proxy to complete the EuroQol?

Yes…….1 **GIVE PROXY FORM TO PROXY**

No……..2 **Subject has no EuroQol response**

7-Day follow up EuroQol

Date of interview: ____/____/____

Interviewer Name: _____

Has patient been discharged?

Yes…….1 **ENSURE PATIENT HAD SELF COMPLETE EUROQOL GIVEN TO THEM ON DISCHARGE, IF NOT POST SELF-COMPLETION EUROQOL TO PATIENT**

No……..2 **CARRY OUT INTERVIEW**

Is patient unconscious?

Yes…….1 **DISCONTINUE INTERVIEW**

No……..2

IF PATIENT IS ABLE TO RESPOND TO INTERVIEWER ASK*: Hello. Thank you for agreeing to take part in this study. We are interested in how you feel today. To find this out we would like you to fill in a short questionnaire. Do you feel able to complete this questionnaire yourself?*

Is patient able to self-complete Euroqol?

Yes…….1 **GIVE PATIENT SELF COMPLETE EUROQOL AND ATTACH COMPLETED FORM TO BACK OF THIS FORM**

No……..2 **COMPLETE SECTION 2**

IF A PROXY INTERVIEW HAS BEEN USED FOR BASELINE AND THE SUBJECT IS ABLE TO GIVE EUROQOL RESPONSES (EITHER BY SELF-COMPLETION OR INTERVIEW) THEN PLEASE ENSURE THAT A PROXY INTERVIEW IS ALSO COMPLETED (IF POSSIBLE)

Section 2 EuroQol by interview

Is patient able to complete euroqol by interview?

Yes…….1 **CARRY OUT EUROQOL INTERVIEW**

No……..2 **COMPLETE SECTION 3**

Section 3 EuroQol by Proxy

Can you identify a suitable proxy to complete the EuroQol? IF PROXY IS USED AND IF A PROXY WAS USED FOR THE BASELINE INTERVIEW THEN ENSURE THAT SAME PROXY IS USED FOR FOLLOW UP.

Yes…….1 **GIVE PROXY FORM TO PROXY**

No……..2 **Subject has no EuroQol response**

28-Day follow up EuroQol

Date of interview: ____/____/____

Interviewer Name: _____

Has patient been discharged?

Yes…….1 **ENSURE PATIENT HAD SELF COMPLETE EUROQOL GIVEN TO THEM ON DISCHARGE, IF NOT POST SELF-COMPLETION EUROQOL TO PATIENT**

No……..2 **CARRY OUT INTERVIEW**

Is patient unconscious?

Yes…….1 **DISCONTINUE INTERVIEW**

No……..2

IF PATIENT IS ABLE TO RESPOND TO INTERVIEWER ASK*: Hello. Thank you for agreeing to take part in this study. We are interested in how you feel today. To find this out we would like you to fill in a short questionnaire. Do you feel able to complete this questionnaire yourself?*

Is patient able to self-complete EuroQol?

Yes…….1 **GIVE PATIENT SELF COMPLETE EUROQOL AND ATTACH COMPLETED FORM TO BACK OF THIS FORM**

No……..2 **COMPLETE SECTION 2**

IF A PROXY INTERVIEW HAS BEEN USED FOR BASELINE AND/OR 7-DAY INTERVIEW AND THE SUBJECT IS ABLE TO GIVE EUROQOL RESPONSES (EITHER BY SELF-COMPLETION OR INTERVIEW) THEN PLEASE ENSURE THAT A PROXY INTERVIEW IS ALSO COMPLETED (IF POSSIBLE)

Section 2 EuroQol by interview

Is patient able to complete EuroQol by interview?

Yes…….1 **CARRY OUT EUROQOL INTERVIEW**

No……..2 **COMPLETE SECTION 3**

Section 3 EuroQol by Proxy

Can you identify a suitable proxy to complete the EuroQol? **IF PROXY IS USED AND IF A PROXY WAS USED FOR THE BASELINE INTERVIEW THEN ENSURE THAT SAME PROXY IS USED FOR FOLLOW UP.**

Yes…….1 **GIVE PROXY FORM TO PROXY**

No……..2 **Subject has no EuroQol response**

EQ - 5D

Self completion Health Questionnaire

(English version for the UK)
(validated for use in Eire)

Name _____ Study Number _____

Admission date ____/____/____

Date of interview ____/____/____

Baseline 1
7-Day 2
28-Day 3

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

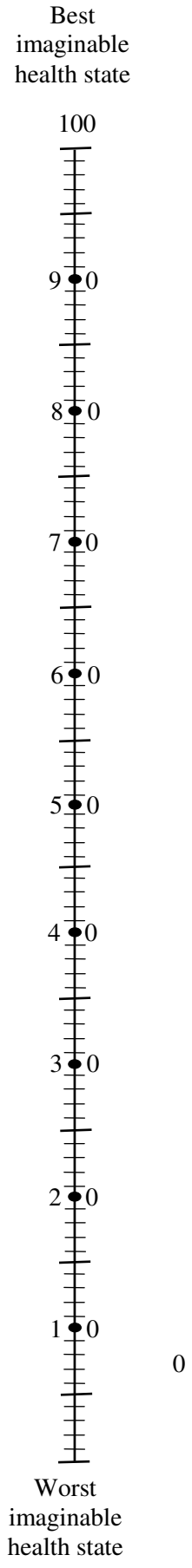
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



APPENDIX I

EQ - 5D

Health Questionnaire

English version for the UK

SCRIPT FOR INTERVIEW ADMINISTRATION

Name: _____ Study Number: _____

Admission date: ____/____/____

Date of interview: ____/____/____

Name of interviewer: _____

Baseline	1
7-Day	2
28-Day	3

APPENDIX I

GENERAL INTRODUCTION

ONLY SECTIONS IN ITALICS ARE TO BE READ OUT

It is suggested that the administrator follows the script of the EQ-5D. Although allowance should be made for the interviewer's particular style of speaking, the wording of the questionnaire instructions should be followed as closely as possible. In the case of the EQ-5D descriptive system on page 2, the precise wording must be followed.

It is recommended that the administrator has a copy of the EQ-5D in front of him or her as it is administered over the telephone. This enables the respondent's answers to be entered directly on the EQ-5D by the administrator on behalf of the respondent (i.e. the appropriate boxes on page 3 are marked and the scale on page 4 is marked at the point indicating the respondents 'own health state today'). If the respondent asks for clarification, the administrator can help by re-reading the question verbatim. The administrator should not try to offer his or her own explanation but suggest that the respondent uses his or her own interpretation.

If the respondent has difficulty with regard to which box to mark, the administrator should repeat the question verbatim and ask the respondent to answer in a way that most closely resembles his or her thoughts about his or her health state today.

We are trying to find out what you think about your health. I will ask you a few brief and simple questions about your own health state today. I will explain the tasks fully as I go along but please interrupt me if you do not understand something or if things are not clear to you. Please also remember that there are no right or wrong answers. We are interested here only in your personal view.

First I am going to read out some questions. Each question has a choice of three answers. Please tell me which answer best describes your own health state today.

Do not choose more than one answer in each group of questions.
NOTE FOR INTERVIEWER: IT MAY BE NECESSARY TO REMIND THE RESPONDENT REGULARLY THAT THE TIMEFRAME IS TODAY. IN ALL CASES PLEASE INDICATE RESPONSES BY CIRCLING ONE NUMBER ONLY FOR EACH QUESTION.

APPENDIX I

Mobility
First I'd like to ask you about mobility. Would you say you have…

1. *No problems in walking about?*
2. *Some problems in walking about?*
3. *Are you confined to bed?*

Self-Care
Next I'd like to ask you about self-care. Would you say you have…

1. *No problems with self-care?*
2. *Some problems washing or dressing yourself?*
3. *Are you unable to wash or dress yourself?*

Usual Activities
Next I'd like to ask you about usual activities, for example work, study, housework, family or leisure activities. Would you say you have: **…**

1. *No problems with performing your usual activities?*
2. *Some problems with performing your usual activities?*
3. *Are you unable to perform your usual activities?*

Pain/Discomfort
Next I'd like to ask you about pain or discomfort. Would you say you have…

1. *No pain or discomfort?*
2. *Moderate pain or discomfort?*
3. *Extreme pain or discomfort?*

Anxiety/Depression

Finally I'd like to ask you about anxiety or depression. Would you say you are…

1. *Not anxious or depressed?*
2. *Moderately anxious or depressed?*
3. *Extremely anxious or depressed?*

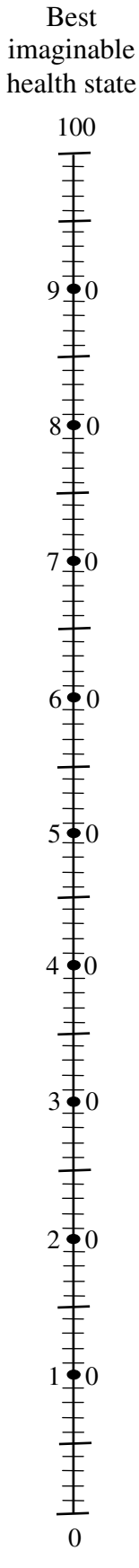
APPENDIX I

I would now like to ask you to do a rather different task.

To help you say how good or bad your health state is, I'd like you to try to picture in your mind a scale that looks a bit like a thermometer. Can you do that? The best health state you can imagine is marked 100 (one hundred) at the top of the scale and the worst state you can imagine is marked 0 (zero) at the bottom.

I would now like you to tell me the point on this scale where you would put your own health state today.

Your own health state today



APPENDIX I

EQ - 5D

Health Questionnaire

English version for the UK

Script for proxy version of the EQ-5D

(Asking the proxy to rate how he or she, (i.e. the proxy),
would rate the subject's health)

Name: _____ Study Number _____

Date on which questionnaire was completed (dd/mm/yy) ___ / ___ / ___

Name of person filling in this questionnaire: _____

Relationship to patient: _____

APPENDIX I

Proxy version of the EQ-5D:

By placing a tick in one box in each group below, please indicate which statements best describe _____health state today.

Do not tick more than one box in each group

Mobility

No problems in walking about ❑

Some problems in walking about ❑

Confined to bed ❑

Self-Care

No problems with self-care ❑

Some problems washing or dressing himself/herself ❑

Unable to wash or dress himself/herself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

No problems with performing his/her usual activities ❑

Some problems with performing his/her usual activities ❑

Unable to perform his/her usual activities ❑

Pain/Discomfort

No pain or discomfort ❑

Moderate pain or discomfort ❑

Extreme pain or discomfort ❑

Anxiety/Depression

Not anxious or depressed ❑

Moderately anxious or depressed ❑

Extremely anxious or depressed ❑

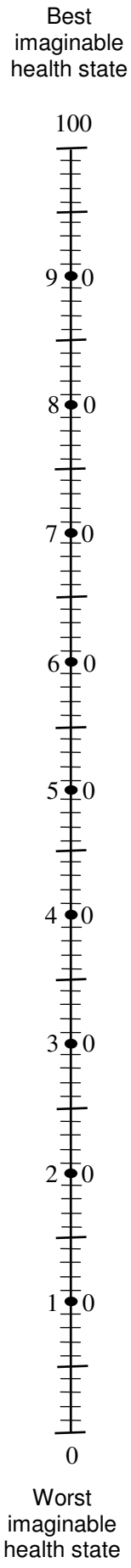
APPENDIX I

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad _____ health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad you think the subject's health state is today.

_____

Health today



A RANDOMISED CONTROLLED TRIAL TO EVALUATE IMPACT OF DIAGNOSTIC TESTING FOR INFLUENZA, RESPIRATORY SYNCYTIAL VIRUS AND STREPTOCOCCUS PNEUMONIAE INFECTION ON THE MANAGEMENT OF ACUTE ADMISSIONS IN THE ELDERLY AND HIGH-RISK ADULTS.

Name _____ **Study Number** _____

EQ - 5D

Self completion Health Questionnaire
(Day 7 Postal)
(English version for the UK)
(validated for use in Eire)

We would like to thank you again for agreeing to take part in the above study. As part of this research we are interested in your health today. For this reason we would like you to complete the following short questionnaire and return it to us in the pre-paid envelope provided. We would be grateful if you could complete this questionnaire as soon as possible. Please return it to us in the pre-paid envelope provided.

Please indicate the date on which you completed this questionnaire:

Date: ____/____/____

APPENDIX I

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

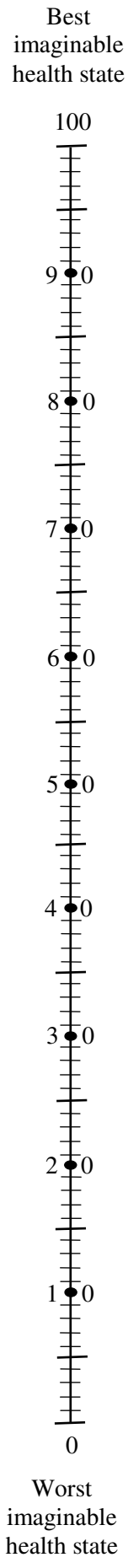
I am extremely anxious or depressed ❑

APPENDIX I

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



APPENDIX I

A RANDOMISED CONTROLLED TRIAL TO EVALUATE IMPACT OF DIAGNOSTIC TESTING FOR INFLUENZA, RESPIRATORY SYNCYTIAL VIRUS AND STREPTOCOCCUS PNEUMONIAE INFECTION ON THE MANAGEMENT OF ACUTE ADMISSIONS IN THE ELDERLY AND HIGH-RISK ADULTS.

Name _____ **Study Number** _____

EQ - 5D

Health Questionnaire
(Day 7 Postal- Proxy)
English version for the UK

Script for proxy version of the EQ-5D

(Asking the proxy to rate how he or she, (i.e. the proxy),
would rate the subject's health)

We would like to thank you again for agreeing to help us with the above study. As part of this research we are interested in _____'s health today. For this reason we would like you to complete the following short questionnaire and return it to us in the pre-paid envelope provided. We would be grateful if you could complete this questionnaire as soon as possible. Please return it to us in the pre-paid envelope provided.

Please indicate the date on which you completed this questionnaire

____ /____ /____

APPENDIX I

By placing a tick in one box in each group below, please indicate which statements best describe _____health state today.

Do not tick more than one box in each group

Mobility

No problems in walking about ❑

Some problems in walking about ❑

Confined to bed ❑

Self-Care

No problems with self-care ❑

Some problems washing or dressing himself/herself ❑

Unable to wash or dress himself/herself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

No problems with performing his/her usual activities ❑

Some problems with performing his/her usual activities ❑

Unable to perform his/her usual activities ❑

Pain/Discomfort

No pain or discomfort ❑

Moderate pain or discomfort ❑

Extreme pain or discomfort ❑

Anxiety/Depression

Not anxious or depressed ❑

Moderately anxious or depressed ❑

Extremely anxious or depressed ❑

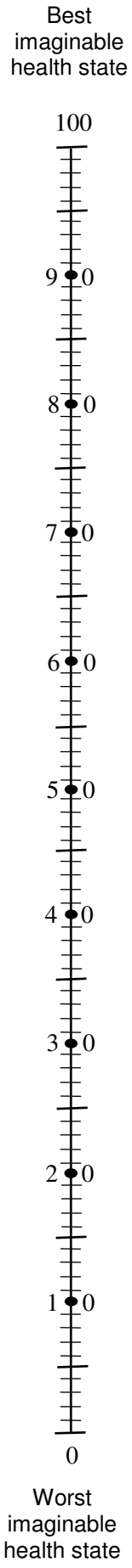
APPENDIX I

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad _____health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad you think the subject's health state is today.

_____

Health today



APPENDIX I

28-Day telephone interview with subjects unable to complete postal questionnaires

Name _____ **Study Number** _____

Admission date ____/____/____ Discharge date ____/____/____

Date of 28 days from admission date ____/____/____

During your recent stay in hospital you kindly agreed to take part in the above study. As part of this research we would like to ask you a few questions about any health care you have received since you were discharged from hospital.

We would also like to ask you a few simple questions about your health today.

Question 1. *Firstly, we would like to ask you if any of the following health care professionals have visited you in your own home since you were discharged from hospital? Remember, here we are only interested in health care you have received in your own home. Have you seen a* **PLEASE READ OUT THE LIST BELOW: IF YES, ASK** *How many times did you see this person?*

☐1	GP	How many times? _____
☐2	District nurse	How many times? _____
☐3	Practice nurse	How many times? _____
☐4	Other nurse	How many times? _____
☐5	Home care worker/ home help	How many times? _____

AT END of LIST ASK. *Apart from the people I have mentioned have you any other health care professionals in your own home?* **IF YES, ASK**: *How many times did you see this person?* **PLEASE KEEP ASKING UNTIL RESPONDENT STATES THEY HAVE SEEN NO OTHER HEALTH CARE PROFESSIONAL.**

☐6	Other person (please specify) _____	How many times? _____
☐7	Other person (please specify) _____	How many times? _____
☐8	Other person (please specify) _____	How many times? _____

Question 2. *We would now like you to think of any health care professionals that you might have seen outside your own home since you were discharged from hospital. Remember, here we are only interested in health care you have received outside your own home. Have you seen a* **READ OUT THE LIST BELOW: IF YES, ASK** *How many times did you see this person?*

☐1	Hospital doctor in outpatients department	How many times? _____
☐2	GP	How many times? _____
☐3	Practice nurse	How many times? _____
☐4	Other nurse	How many times? _____
☐5	A&E department	How many times? _____

Apart from the people I have mentioned have you visited any other health care professionals outside your home? **IF YES, ASK:** *How many times did you see this person?* **PLEASE KEEP ASKING UNTIL RESPONDENT STATES THEY HAVE SEEN NO OTHER HEALTH CARE PROFESSIONAL.**

☐6	Other (please specify) _____	How many times? _____
☐7	Other (please specify) _____	How many times? _____
☐8	Other (please specify) _____	How many times? _____

Question 3. *Since your discharge from hospital have you had any extra medicines prescribed for you? Please do not include any medicines you were prescribed in hospital, or any medicines that you regularly received before your stay in hospital. We are only interested in extra medicines that have been prescribed since you were discharged from hospital.*

Yes ☐1
No ☐2

IF YES, ASK *How many new medicines have you been prescribed?* _____

APPENDIX I

For each new medicine could you tell us the name of this medicine and how long (in days) the prescription was for?

	Name of Medicine	How long for?
1		
2		
3		
4		
5		

Question 4. *Since your discharge from hospital have you bought any non-prescription medicines 'over-the-counter'; for example, in chemists, supermarkets, or other shops. Please also include any medicines that were bought for you by other people. Again, we are interested only in the period since your discharge from hospital.*

Yes ☐1
No ☐2

IF YES, ASK *How many 'over-the-counter' medicines have you purchased or had purchased for you since you were discharged from hospital?* _____

For each medicine could you tell us the name of this medicine, the number of items (i.e. packets, bottles, or tubes) and the approximate packet size?

	Name of Medicine	Number of items	Approximate packet size
1			
2			
3			
4			
5			

APPENDIX I

EuroQol

We are trying to find out what you think about your health. I will ask you a few brief and simple questions about your own health state today. I will explain the tasks fully as I go along but please interrupt me if you do not understand something or if things are not clear to you. Please also remember that there are no right or wrong answers. We are interested here only in your personal view.
First I am going to read out some questions. Each question has a choice of three answers. Please tell me which answer best describes your own health state today.
Do not choose more than one answer in each group of questions.
NOTE FOR INTERVIEWER: IT MAY BE NECESSARY TO REMIND THE RESPONDENT REGULARLY THAT THE TIMEFRAME IS TODAY. IN ALL CASES PLEASE INDICATE RESPONSES BY CIRCLING ONE NUMBER ONLY FOR EACH QUESTION.

Mobility
First I'd like to ask you about mobility. Would you say you have…

1. *No problems in walking about?*
2. *Some problems in walking about?*
3. *Are you confined to bed?*

Self-Care
Next I'd like to ask you about self-care. Would you say you have…

1. *No problems with self-care?*
2. *Some problems washing or dressing yourself?*
3. *Are you unable to wash or dress yourself?*

Usual Activities
Next I'd like to ask you about usual activities, for example work, study, housework, family or leisure activities. Would you say you have: **…**

1. *No problems with performing your usual activities?*
2. *Some problems with performing your usual activities?*
3. *Are you unable to perform your usual activities?*

Pain/Discomfort
Next I'd like to ask you about pain or discomfort. Would you say you have…

1. *No pain or discomfort?*
2. *Moderate pain or discomfort?*
3. *Extreme pain or discomfort?*

Anxiety/Depression

Finally I'd like to ask you about anxiety or depression. Would you say you are…

1. *Not anxious or depressed?*
2. *Moderately anxious or depressed?*
3. *Extremely anxious or depressed?*

APPENDIX I

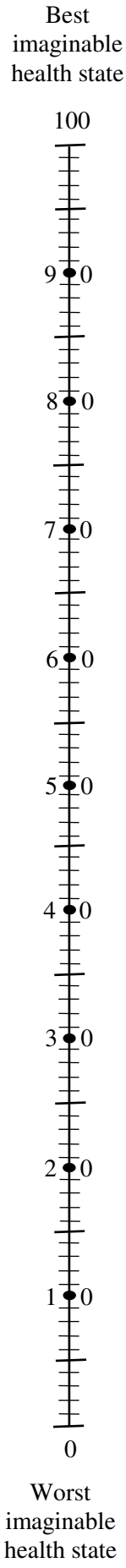
I would now like to ask you to do a rather different task.

To help you say how good or bad your health state is, I'd like you to try to picture in your mind a scale that looks a bit like a thermometer. Can you do that? The best health state you can imagine is marked 100 (one hundred) at the top of the scale and the worst state you can imagine is marked 0 (zero) at the bottom.

I would now like you to tell me the point on this scale where you would put your own health state today.

Your own health state today

Finally, we would like to thank you for your help in completing this questionnaire.



APPENDIX I

HOSPIAL HEADED NOTEPAPER

Day 28 postal questionnaire

A RANDOMISED CONTROLLED TRIAL TO EVALUATE IMPACT OF DIAGNOSTIC TESTING FOR INFLUENZA, RESPIRATORY SYNCYTIAL VIRUS AND STREPTOCOCCUS PNEUMONIAE INFECTION ON THE MANAGEMENT OF ACUTE ADMISSIONS IN THE ELDERLY AND HIGH-RISK ADULTS.

Name _____ **Study Number** _____

Admission date ____/____/____ Discharge date ____/____/____

Date of 28 days from admission date ____/____/____

During your recent stay in hospital you kindly agreed to take part in the above study. As part of this research we would like to ask you a few questions about any health care you have received since you were discharged from hospital

We would also like to ask you a few simple questions about your health today.

Question 1. Firstly, we would like to ask you if any of the following health care professionals have visited you in your <u>own home</u> since you were discharged from hospital? For each type of person, please tick the box if you saw this health care professional and tell us how many times you saw this person. . Remember, here we are only interested in health care you have received in your <u>own home</u>.

☐1	GP	How many times? _____
☐2	District nurse	How many times? _____
☐3	Practice nurse	How many times? _____
☐4	Other nurse	How many times? _____
☐5	Home care worker/ home help	How many times? _____
☐6	Other person (please specify) _____	How many times? _____
☐7	Other person (please specify) _____	How many times? _____
☐8	Other person (please specify) _____	How many times? _____

Question 2. We would now like you to think of any health care professionals that you might have seen outside your own home since you were discharged from hospital. For each type of person, please tick the box if you saw this health care professional and tell us how many times you saw this person. Remember, here we are only interested in visits you have made to receive healthcare outside your home.

☐1	Hospital doctor in outpatients department	How many times? _____
☐2	GP	How many times? _____
☐3	Practice nurse	How many times? _____
☐4	Other nurse	How many times? _____
☐5	A&E department	How many times? _____
☐6	Other (please specify) _____	How many times? _____
☐7	Other (please specify) _____	How many times? _____
☐8	Other (please specify) _____	How many times? _____

Question 3. Since your discharge from hospital have you had any extra medicines prescribed for you?

(Please do not include any medicines you were prescribed in hospital, or any medicines that you regularly received before your stay in hospital. We are only interested in extra medicines that have been prescribed since you were discharged from hospital.)

YES ☐1
NO ☐2

If YES: How many new medicines have you been prescribed? _____
For each new medicine could you tell us the name of this medicine and how long (in days) the prescription was for? Please place your answers in the boxes below

	Name of Medicine	How long for?
1		
2		
3		
4		
5		

Question 4. Since your discharge from hospital have you bought any non-prescription medicines 'over-the-counter'; for example, in chemists, supermarkets, or other shops. Please also include any medicines that were bought for you by other people. Again, we are interested only in the period since your discharge from hospital.

YES ☐1
NO ☐2

If yes, how many 'over-the-counter' medicines have you purchased or had purchased for you since you were discharged from hospital? _____

For each medicine could you tell us the name of this medicine, the number of items (i.e. packets, bottles, or tubes) and the approximate packet size. Please place your answers in the boxes below

	Name of Medicine	Number of items	Approximate packet size
1			
2			
3			
4			
5			

Question 5. We would now like you to think about your health today. By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑
I have some problems in walking about ❑
I am confined to bed ❑

APPENDIX I

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

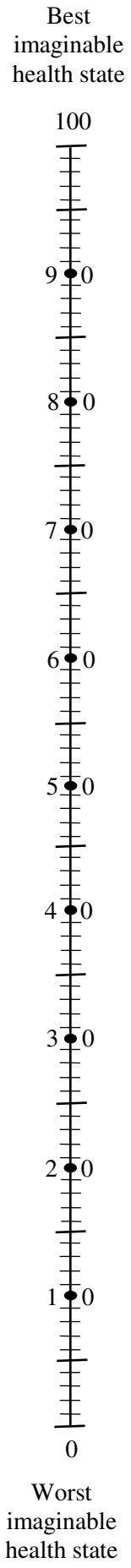
APPENDIX I

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today

Finally, we would like to thank you for your help in completing this questionnaire. Please return it to us in the prepaid envelope provided.



APPENDIX II

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000.

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data. 2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty. 3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient." 4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects. 5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society. 6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality. 7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens. 8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care. 9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject. 11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation. 12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected. 13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects. 14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration. 15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent. 16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available. 17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results. 18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers. 19. Medical research is only justified if there is a reasonable likelihood that the populations in

which the research is carried out stand to benefit from the results of the research. 20. The subjects must be volunteers and informed participants in the research project. 21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject. 22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed. 23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship. 24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons. 25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative. 26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate. 27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects. 29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists. 30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study. 31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship. 32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

7.10.2000 09h14

APPENDIX III

ENROLMENT LOG (LEICESTER ROYAL INFIRMARY)
(PLEASE PRINT THE FOLLOWING INFORMATION USING BLACK INK)

Trial identification number	Surname	First name	Sex (M/F)	Address	Post-code	Date of birth (dd/mmm/yy)	Date of entry into study (dd/mmm/yy)
1-0001							
1-0002							
etc……							

ENROLMENT LOG (GLENFIELD HOSPITAL)
(PLEASE PRINT THE FOLLOWING INFORMATION USING BLACK INK)

Trial identification number	Surname	First name	Sex (M/F)	Address	Post-code	Date of birth (dd/mmm/yy)	Date of entry into study (dd/mmm/yy)
2-0001							
2-0002							
etc……							

ENROLMENT LOG (LEICESTER GENERAL HOSPITAL)
(PLEASE PRINT THE FOLLOWING INFORMATION USING BLACK INK)

Trial identification number	Surname	First name	Sex (M/F)	Address	Post-code	Date of birth (dd/mmm/yy)	Date of entry into study (dd/mmm/yy)
3-0001							
3-0002							
etc……							

APPENDIX IV

HOSPITAL HEADED PAPER

PATIENT INFORMATION SHEET

A RANDOMISED CONTROLLED TRIAL TO EVALUATE IMPACT OF DIAGNOSTIC TESTING FOR INFLUENZA, RESPIRATORY SYNCYTIAL VIRUS AND STREPTOCOCCUS PNEUMONIAE INFECTION ON THE MANAGEMENT OF ACUTE ADMISSIONS IN THE ELDERLY AND HIGH-RISK ADULTS.

Introduction

You are being invited to take part in a research study, to evaluate new diagnostic tests. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

The purpose of this study is to evaluate new tests for three chest germs, influenza, RSV virus (respiratory syncytial virus) and the pneumococcus. The usefulness of these tests will be compared to usual laboratory methods that are much slower and may be less accurate. We want to find out whether the new tests help patients improve more quickly and improve the use of rooms that confine infection.

Why have I been chosen?

You have been chosen because you have a condition that could be caused by a chest germ. In total we would like to study around 3000 people like you to get a better picture of the potential benefits of using the new tests.

Do I have to take part?

Your participation in this study is entirely voluntary. It is up to you to decide whether or not to take part. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive now or in the future.

What will happen to me if I take part?

You will be investigated and treated by the medical team caring for you, according to their assessment, whether you take part or not.

If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. You will see the Study Nurse today and on up to six further occasions, depending on the period you spend in hospital, over the course of four weeks. All the visits will be brief.

APPENDIX IV

Today, Day 1:

If you decide to take part in the study, an informed consent form must be signed by you in the presence of the study doctor or a member of the study team. You will be asked about past medical problems, vaccinations against influenza and *S. pneumoniae,* details of your current illness, plus any medicines that you are currently taking, and things that might increase the risk of infection. You will also be required to give a 25ml blood sample from the vein in your elbow (about five teaspoonfuls), a specimen of phlegm and a urine sample, and your nose will be swabbed – this involves collecting a small sample of fluid and cells from inside your nose. Your health state today will be assessed by a short questionnaire. A letter will be sent to your GP, with your permission, saying that you are taking part in this study.We may contact your GP for medical details, such as your medications, or immunisation history that you are unable to recall.

Follow-up assessments, Days 2, 3, 4, 7, 10, and 28
The follow-up assessment on these days is mainly to record your progress from the medical and nursing notes, including the tests done on your behalf, where you are being nursed, the treatment that you are receiving, and presence of fever.

Your health state will be assessed on days 7 and 28, with a short questionnaire during a visit to the ward, or by post or by telephone. A 10ml blood sample(2 teaspoons) will be collected from you for antibody studies on day 10, either on the ward, or at home. On Day 28, you will be asked about any visits to see your GP or hospital doctor, and any treatments that you received from them.

What do I have to do?
Between the time that you start on the study and complete it 28 days later you will be asked to allow us access to your hospital records, answer short questionnaires about your health state, provide a specimen of phlegm, a urine sample, a nose and throat swab and two small blood samples, and provide information about any follow-up visits.

What is the drug or procedure that is being tested?
We are not testing any new drug or clinical procedure.

What are the alternatives for diagnosis?
We are testing 'bedside' diagnostic tests in one third of the participants (Group 1); rapid laboratory tests in another third (Group 2); and usual laboratory methods in the remainder (Group 3). However, ALL participants will have their samples tested on admission by the usual laboratory methods, so everyone – including those in Groups 1 and 2 – will be investigated according to the current standard of care.

What studies will you do with my specimens?
Depending on your study group, we will do the above tests straight away to see whether you are infected with influenza, RS virus, or the pneumococcus. However, all tests will ultimately be done on stored specimens from everyone. Stored specimens may undergo additional tests for other chest germs to examine the accuracy of the new tests.

What are the possible disadvantages and risks of taking part?

A disadvantage of taking part is the inconvenience of giving information and samples. Occasionally, blood collection causes pain and bruising. It may also cause light-headedness and, rarely, fainting or infection. The collection of a nasal swab may cause some transient minor irritation.

Early identification of the pneumococcus infection might lead your medical team to treat you with the recommended antibiotic for this germ. While this is likely to be beneficial, it could be detrimental if you were infected with several different germs. We will monitor for this unlikely event, to make sure that patients are not harmed by earlier test results.

What are the possible benefits of taking part?

A possible benefit is the earlier diagnosis of infection with 'flu', RS virus, or the pneumococcus, with treatment given appropriately. This may improve your quality of life by cutting side - effects associated with the use of antibiotics. People may benefit from a lower risk of cross-infection in the hospital through more efficient use of isolation facilities. You may benefit from an increased level of monitoring of your illness, with earlier treatment of any complications. Should the tests be found useful in this study, then you and others may benefit from their routine use.

What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the subject that is being studied. If this happens, the Study Nurse will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw we will ensure that your normal care continues. If you decide to continue in the study you will be asked to sign an updated consent form.

What happens when the research study stops?

Treatment is not being provided as part of this study, so neither you nor anyone else will be disadvantaged when the study stops.

What if something goes wrong?

We are not testing any medicines, so adverse reactions to a study drug will not occur. The collection of blood and the nose sample are routine procedures and are not likely to cause harm. If taking part in this research project harms you, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you.

Will my taking part in this study be kept confidential?

Your diagnostic samples and the accompanying investigation request forms that are sent to laboratories at the Leicester Royal Infirmary, will be labelled with your name, address, sex, date of birth, and hospital number in the standard way. Any samples that are stored in freezers for tests at the Health Protection Agency Laboratory, London, will be identified only by your study number, date of birth, and initials.

Your study details will be stored at the Leicester Royal Infirmary, or a designated storage site for the University Hospitals of Leicester NHS Trust, and will be labelled with your name, address, sex, date of birth, and hospital number.

Any information given by you to the Study Nurse is confidential, and your medical details will be kept strictly confidential. However, authorised independent safety monitors, the sponsors, the funding agency, or their representatives, will be allowed access to your medical records relating to

the trial. This is to ensure that the study is being carried out in accordance with current laws and to ensure that patient welfare is not adversely affected by the study.

For the purposes of confidentiality you will only be identified on password-protected computers by a number and your initials on any information used for the trial.

What will happen to the results of the research study?

The results of this study will be published as a report to the Department of Health, and in medical journals. We will provide you with your results.

Who is organising and funding the research?

The study is being organised by the Principal Investigator, Professor Karl Nicholson, together with co-investigators at the University Hospitals of Leicester NHS Trust, the University of Leicester, and the Health Protection Agency, London. The study is funded by the UK Department of Health Research and Development Health Technology Assessment Programme.

Who is the sponsor of this study?

This study is sponsored by the University Hospitals of Leicester NHS Trust.

Who has reviewed the study?

The study has been peer-reviewed by the UK Department of Health Research and Development Health Technology Assessment Programme, and by the Leicester Research Ethics Committee

Who to Contact

If you have any further questions, either now or later, or in case of an emergency, please do not hesitate to contact the following medical staff:

Professor Karl G Nicholson MD, FRCP, FRCPath, MFPHM, Professor of Infectious Diseases, Leicester Royal Infirmary, Infirmary Square, Leicester LE1 5WW.

Direct dial telephone: 0116 2586164.
Mobile telephone: 07880746939

Thank you for taking the time to read this information. If you decide to take part in this study please keep a copy of this for your information

APPENDIX IVa

HOSPITAL HEADED PAPER

PATIENT INFORMATION SHEET (SYNOPSIS)

A Randomised Controlled Trial to Evaluate Impact of Diagnostic Testing for Influenza, Respiratory Syncytial Virus and Streptococcus Pneumoniae Infection on the Management of Acute Admissions in the Elderly and High-Risk Adults.

Introduction

You are being invited to take part in a research study.

What is the purpose of the study?

The purpose of the study is to evaluate new rapid tests for three chest germs.

Why have I been chosen?

You have been chosen because you may have a condition caused by a chest germ.

Do I have to take part?

Your participation in this study is entirely voluntary. If you take part you are free to withdraw at any time without giving a reason.

What will happen to me if I take part?

You will be investigated and treated as usual by the medical team caring for you.

You will be asked to sign a consent form. We will collect a nose and throat swabs, two blood samples, a urine sample, and some general information about you when you are feeling better.

The study involves following your care and progress for 28 days.

What do I have to do?

You will be asked to provide the specimens for diagnosis, allow us access to your medical records, and provide some general information.

What is the drug or procedure that is being tested?

We are not testing any new drug or clinical procedure.

What are the alternatives for diagnosis?

We are comparing new rapid diagnostic tests for three germs with existing tests. Everyone will have their samples tested normally. Two in three people will be tested by the rapid methods as well.

What are the possible disadvantages and benefits of taking part?

No specific risks are anticipated from participation in this study. A possible benefit is the earlier diagnosis of your illness.

Who has reviewed the study?

The study has been peer-reviewed by the UK Department of Health Research and Development Health Technology Assessment Programme, and by the Leicester Research Ethics Committee

Who to Contact

If you have any further questions, either now or later, you can contact the following:

Professor Karl G Nicholson, Leicester Royal Infirmary, Infirmary Square, Leicester LE1 5WW.
Direct dial telephone: 0116 2586164. Mobile telephone: 07880746939

If you decide to take part in this study please keep a copy of this for your information.

-APPENDIX V

HOSPITAL HEADED PAPER

INFORMATION SHEET (RELATIVE OR CARER)

A RANDOMISED CONTROLLED TRIAL TO EVALUATE IMPACT OF DIAGNOSTIC TESTING FOR INFLUENZA, RESPIRATORY SYNCYTIAL VIRUS AND STREPTOCOCCUS PNEUMONIAE INFECTION ON THE MANAGEMENT OF ACUTE ADMISSIONS IN THE ELDERLY AND HIGH-RISK ADULTS.

Introduction

We are inviting patients to take part in a research study, to evaluate new diagnostic tests. Some patients are too breathless or confused to judge whether to take part or not. For such people we are seeking the agreement of a relative or carer on the patient's behalf. We will subsequently invite patients to continue in the study when they can decide for themselves. Before you decide today it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to make a decision.

What is the purpose of the study?

The purpose of this study is to evaluate new tests for three chest germs, influenza, RS virus (respiratory syncytial virus) and the pneumococcus. The usefulness of these tests will be compared to usual laboratory methods that are much slower and may be less accurate. We want to find out whether the new tests help patients improve more quickly and improve the use of rooms that confine infection.

Why has this patient been chosen?

This patient has been chosen because he or she has a condition that could be caused by a chest germ. In total we would like to study approximately 3000 people to get a better picture of the potential benefits of using the new tests.

Does this patient have to take part?

Participation in this study by patients who are too poorly to judge for themselves is entirely at the discretion of a relative or carer. It is up to you to decide whether or not this relative, friend or patient can take part. If you agree, you are still free to withdraw this person from the study at any time and without giving a reason. This will not affect the standard of care that he or she will receive now or in the future.

What will happen to people who take part?

Participants will be investigated and treated by the medical team caring for them, according to the medical team's assessment, whether this person takes part or not.

If you decide whether or not your relative, friend or patient can take part, you will be given this information sheet to keep and be asked to sign an assent form. The patient will see the Study Nurse today and on up to six further occasions, depending on the period he or she spends in hospital over the course of four weeks. All the visits will be brief.

Today, Day1:

If you decide that your relative, friend or patient can take part we will gather information about his or her past medical problems, vaccinations against influenza and *S. pneumoniae,* details of their current illness, plus any medicines that he or she is currently taking, and things that might increase the risk of infection. We will take a 25ml blood sample from the vein in his or her elbow (approx. five teaspoonfuls), a specimen of phlegm and a urine sample, and swab his or her nose – this involves collecting a small sample of fluid and cells from inside the nose. His or her health state today will be assessed by a short questionnaire. A letter will be sent to his or her GP, with your permission, stating that he or she is taking part in this study. We may contact the GP for medical details, such as medications, or immunisation history.

Follow-up assessments, Days 2, 3, 4, 7, 10, and 28

The follow-up assessment on these days is mainly to record his or her progress from the medical and nursing records, including the tests done on his or her behalf, where he or she being nursed, the treatment that he or she is receiving, and presence of fever.

His or her health state will be assessed by a short questionnaire on days 7 and 28, either during a visit on the ward, or by post or by telephone if he or she has been discharged. A 10ml blood sample will be collected from your relative, friend, or patient for antibody studies on day 10, either on the ward, or at home if he or she has been discharged. At completion of the study on Day 28, we will ask about any visits he or she had with their general practitioner or hospital doctor, and any treatments that he or she received from them.

What does he or she have to do?

Between the time that a participant starts on the study and completes it 28 days later, we ask that he or she will comply with the requirements of the study protocol, specifically to provide a specimen of phlegm, a urine sample, a nose and throat swab and two small blood samples.

What is the drug or procedure that is being tested?

We are not testing any new drug or clinical procedure.

What are the alternatives for diagnosis?

We are testing 'bedside' diagnostic tests in one third of the participants (Group 1); rapid laboratory tests in another third (Group 2); and usual diagnostic methods in the remainder (Group 3). However, ALL participants will have their samples tested on admission by the usual laboratory methods, so everyone – including those in Groups 1 and 2 – will be investigated according to the current standard of care

What studies will you do with the specimens?

Depending on the study group, we will do the above tests straight away to see whether participants are infected with influenza, RS virus, or the pneumococcus. However, all tests will ultimately be done on stored specimens from everyone. Stored specimens may undergo additional diagnostic tests for other chest germs to examine the accuracy of the new tests.

What will you do if the patient decides not to continue with the study?

We will destroy all stored specimens from the participant and will withdraw him or her from the study.

What are the possible disadvantages and risks of taking part?

A disadvantage of taking part is the inconvenience of giving information and samples.Occasionally, blood collection causes pain and bruising. It may also cause light-headedness and, rarely, fainting or infection. The collection of a nasal swab may cause some transient minor irritation. Early identification of the pneumococcus infection might lead the medical team treating participants with the recommended 'narrow spectrum'antibiotic for this germ. While this is likely to be beneficial, it could be detrimental if participants were infected with several different germs. We will monitor for this unlikely event to make sure that patients are not adversely harmed by earlier test results.

What are the possible benefits of taking part?

A possible benefit to participants is the earlier diagnosis of 'flu', RS virus, and the pneumococcus, with treatment given appropriately. This may improve their quality of life by cutting side-effects associated with the use of antibiotics. People may benefit from a lower risk of cross-infection in the hospital through more efficient use of isolation facilities. They may benefit from an increased level of monitoring of their illness, with earlier treatment of any complications. Should the tests be found useful in this study, then participants and others may benefit from their routine use.

What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the subject that is being studied. If this happens, the Study Nurse will tell you about it and discuss with you whether you want your relative, friend or patient to continue in the study. If you decide that the participant should continue in the study you will be asked to sign an updated assent form. Similarly if the participant improves so that they able to decide whether to continue or not, the Study Nurse will inform them of the study and seek signed informed consent from the patient. If a participant is withdrawn from the study we will ensure that his or her normal care continues.

What happens when the research study stops?

Treatment is not being provided as part of this study, so neither the participant nor anyone else will be disadvantaged when the study stops.

What if something goes wrong?

We are not testing any medicines, so adverse reactions to a study drug will not occur. The collection of blood and the nose sample are routine procedures and are not likely to cause any harm. If taking part in this research project harms participants, there are no special compensation arrangements. If a participant is harmed due to someone's negligence, then he or she may have grounds for a legal action but they may have to pay for it. Regardless of this, if anyone wishes to complain, or have any concerns about any aspect of the way that any participant has been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available.

Will this person's participation in this study be kept confidential?

The diagnostic samples and the accompanying investigation request forms that are sent to laboratories at the Leicester Royal Infirmary, will be labelled with the participant's name, address, sex, date of birth, and hospital number in the standard way. Any samples that are

stored in freezers for tests at the Health Protection Agency, London, will be identified only by the participant's study number, date of birth, and initials.

Participant's study details will be stored at the Leicester Royal Infirmary, or a designated storage site for the University Hospitals of Leicester NHS Trust, and will be labelled with their name, address, sex, date of birth, and hospital number.

Any information given to the Study Nurse is confidential, and participant's medical details will be kept strictly confidential. However, authorised independent safety monitors, the sponsor, the funding agency, or their representatives, will be allowed access to your medical records relating to the trial. This is to ensure that the study is being carried out in accordance with current laws and to ensure that patient welfare is not adversely affected by the study.

For the purposes of confidentiality participants will only be identified on password-protected computers by a number and their initials on any information used for the trial.

What will happen to the results of the research study?

The results of this study will be published as a report to the Department of Health, and in peer-reviewed medical journals. We will provide participants with their results.

Who is organising and funding the research?

The study is being organised by the Principal Investigator, Professor Karl Nicholson, together with co-investigators at the University Hospitals of Leicester NHS Trust, the University of Leicester, and the Health Protection Agency, London. The study is funded by the UK Department of Health Research and Development Health Technology Assessment Programme.

Who is the sponsor of this study?

This study is sponsored by the University Hospitals of Leicester NHS Trust.

Who has reviewed the study?

The study has been peer-reviewed by the UK Department of Health Research and Development Health Technology Assessment Programme, and by the Leicester Research Ethics Committee.

Who to Contact

If you have any further questions, either now or later, or in case of an emergency, please do not hesitate to contact the following medical staff:

Professor Karl G Nicholson MD, FRCP, FRCPath, MFPHM, Professor of Infectious Diseases, Leicester Royal Infirmary, Infirmary Square, Leicester LE1 5WW.

Direct dial telephone: 0116 2586164.
Mobile telephone: 07880746939

Thank you for taking the time to read this information. Please keep a copy of this for your information.

APPENDIX VI

HOSPITAL HEADED PAPER

STATEMENT OF CONSENT

A RANDOMISED CONTROLLED TRIAL TO EVALUATE IMPACT OF DIAGNOSTIC TESTING FOR INFLUENZA, RESPIRATORY SYNCYTIAL VIRUS AND STREPTOCOCCUS PNEUMONIAE INFECTION ON THE MANAGEMENT OF ACUTE ADMISSIONS IN THE ELDERLY AND HIGH-RISK ADULTS.

Please initial box

1. I confirm that I have read and understand the information sheet dated *08/07/05 version 2* for the above study and have had the opportunity to ask questions ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that sections of my medical notes may be looked at by authorised independent safety monitors, the sponsors, the funding agency, or their representatives, for purposes relating to the study. ☐

4. I agree to allow the blood, urine, sputum, and nasal samples to be taken from me and allow their use in medical research as described in the Patient Information Sheet. ☐

5. I agree to my GP being informed of my participation in this study and contacted for details of my past medical history. ☐

6. I agree to take part in the study. ☐

I discussed the study with: _____

_____	_____	_____
Patient's Name (Print)	Patient's Signature	Date
_____	_____	_____
Name of person taking consent	Signature	Date
_____	_____	_____
Investigator's Name (Print)	Investigator's Signature	Date

APPENDIX VII

HOSPITAL HEADED PAPER
Statement of Consent

ASSENT BY A RELATIVE OR CARER

A RANDOMISED CONTROLLED TRIAL TO EVALUATE IMPACT OF DIAGNOSTIC TESTING FOR INFLUENZA, RESPIRATORY SYNCYTIAL VIRUS AND STREPTOCOCCUS PNEUMONIAE INFECTION ON THE MANAGEMENT OF ACUTE ADMISSIONS IN THE ELDERLY AND HIGH-RISK ADULTS.

Please initial box

1. I confirm that I have read and understand the information sheet dated *08/07/05 version 2* for the above study and have had the opportunity to ask questions ☐

2. I understand that participation is voluntary and that I can withdraw my assent on behalf of the participant at any time, without giving any reason, without the participant's medical care or legal rights being affected. ☐

3. I understand that sections of the participant's medical notes may be looked at by authorised independent safety monitors, the sponsors, the funding agency, or their representatives, for purposes relating to the study. ☐

4. I agree to allow the blood, urine, sputum, and nasal samples to be taken from the participant and allow their use in medical research as described in the Patient Information Sheet. ☐

5. I agree to the participant' GP being informed of his/her participation in this study and contacted for details of his/her past medical history. ☐

6. I agree to the participant taking part in the study ☐

I discussed the study with: _____

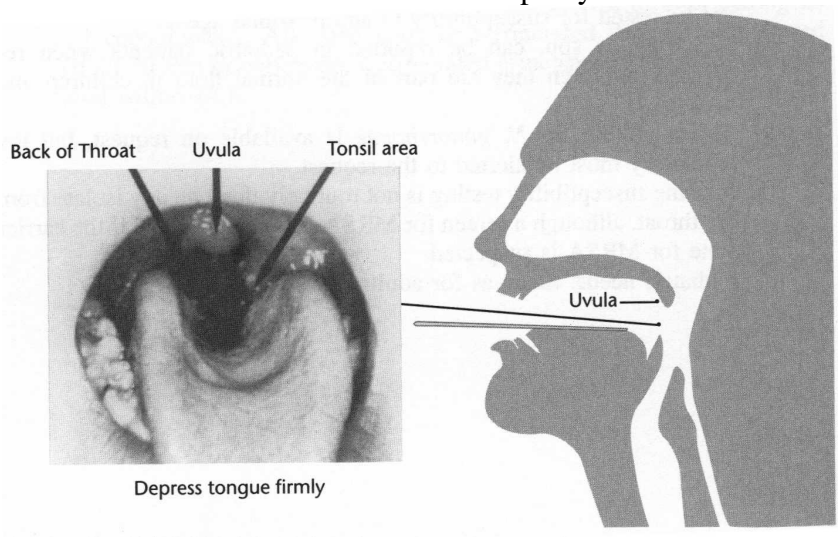
_____	_____	_____
Name of relative or carer (Print)	Signature of relative or carer	Date
_____	_____	_____
Name of person taking consent	Signature	Date
_____	_____	_____
Investigator's Name (Print)	Investigator's Signature	Date

Participant's Name (Print): _____

Nasopharyngeal specimens for the isolation of influenza or RSV.

Cases of suspected influenza or RSV (acute respiratory tract infection or acute bronchitis within five days of onset of illness) are asked for a combined nose & throat swab specimen. A good specimen for the detection of influenza or RSV must contain a substantial number of respiratory epithelial cells, which are mainly obtained from the nasal swab. A throat swab alone will contain mainly squamous epithelial cells in which influenza does not replicate

- A single swab with cotton wool bud is inserted in one nostril and rubbed against and above the nasal turbinates.
- A second swab is used to abrade the tonsils and pharynx.



- Place both swabs in the **same** bijou bottle of virus transport medium.
- Break off the swab sticks (scissors may be used).
- Screw lid tightly onto the bottle.

- Label bottle with patient ID and DOB

APPENDIX VIII

A form is enclosed which specifies:

1. Patient Identification Number
2. Initials
3. Date of birth
4. Sex
5. Date sample taken

NB Please fill in a form for each patient and make sure the patient Identification number and date of birth is also on the sample bijou bottle using the label provided.

Then:

- The bottles should be placed in the white screw cap container. (Although you can put 2 bottles into each container, therefore sending 4 samples per box, do not wait until you have 4 samples to return, simply send the box with the day's samples even if this is only one sample).
- The white containers are then placed into the small box and sealed in the addressed plastic envelope provided, along with the request form.
- These envelopes can then be returned to the laboratory by posting in the normal way, as they are able to fit through the post box.

If you are not able to transport the specimen immediately then they should be kept in a fridge at +4^{o}C and sent to the laboratory at the earliest opportunity. However, please note that in order to recover virus from these samples it is important the laboratory receive samples immediately.

Any further information or help can be obtained by phoning the Health Protection Agency laboratory on:

0208 327 6078 or e-mail rreith@hpa.org.uk

APPENDIX IX

QUICKVUE
Influenza A+B test

PRINCIPLE OF THE TEST

The QuickVue Influenza A+B Test involves the extraction of influenza A and B viral antigens. The patient specimen is placed in the Extraction Reagent Tube, during which time the virus particles in the specimen are disrupted, exposing internal viral nucleoproteins. After extraction, the Test Strip is placed in the Extraction Reagent Tube where nucleoproteins in the specimen will react with the reagents in the Test Strip.

If the extracted specimen contains influenza antigens, a pink-to-red Test Line along with a blue procedural Control Line will appear on the Test Strip indicating a positive result. If influenza type A or type B antigens are not present, or are present at very low levels, only a blue procedural Control Line will appear.

REAGENTS AND MATERIALS SUPPLIED

25-Test Kit: Catalog Number 20183

- Shelf box containing:
  - Individually Packaged Test Strips (25): Mouse monoclonal anti- influenza A and anti-influenza B antibodies
  - Extraction Tubes (25): Lyophilized buffer with detergents and reducing agents
  - Disposable Droppers (25)
  - Sterile Swabs (25)
  - Positive Influenza Type A Control Swab (1): Swab is coated with non-infectious recombinant influenza A antigen
  - Positive Influenza Type B Control Swab (1): Swab is coated with non-infectious recombinant influenza B antigen
  - Negative Control Swab (1): Swab is coated with formalin-inactivated, non-infectious *Streptococcus C* antigen
  - Package Insert (1)
  - Procedure Card (1)

MATERIALS NOT SUPPLIED

- Specimen containers
- Timer or watch

WARNINGS AND PRECAUTIONS

- The QuickVue Influenza A+B Test is for *in vitro* diagnostic use.
- Do not use the kit contents beyond the expiration date printed on the outside of the box.
- Use appropriate precautions in the collection, handling, storage, and disposal of patient samples and used kit contents.[2] Discard used material in a proper biohazard or sharps container.
- The Test Strip must remain sealed in the protective foil pouch until use.
- The Extraction Reagent Solution contains a salt solution. If the solution contacts the skin or eye, flush with copious amounts of water.
- To obtain accurate results, you must follow the Package Insert.

SPECIMEN COLLECTION

Nasal Swab Sample:
For proper test performance, use the swabs supplied in the kit.
To collect a nasal swab sample, insert the sterile swab into the nostril that presents the most secretion under visual inspection. Using gentle rotation, push the swab until resistance is met at the level of the turbinates (less than one inch into the nostril). Rotate the swab a few times against the nasal wall.

SAMPLE TRANSPORT AND STORAGE

Samples should be tested as soon as possible after collection. Do not use any kind of transport media to store or transport samples. Samples may be stored refrigerated (2–8°C), or at room temperature (15–30°C), in a clean, dry, closed container for up to eight hours prior to testing.

QUALITY CONTROL

Built-in Control Features
The QuickVue Influenza A+B Test contains built-in procedural control features. The manufacturer's recommendation for daily control is to document these built-in procedural controls for the first sample tested each day.

The two-color result format provides a simple interpretation for positive and negative results. The appearance of a blue procedural Control Line provides several forms of positive control by demonstrating sufficient flow has occurred and the functional integrity of the Test Strip was maintained. **If the blue procedural Control Line does not develop at 10 minutes, the test result is considered invalid.**

A built-in negative control is provided by the clearing of red background color, verifying that the test has been performed correctly. Within 10 minutes, the result area should be white to light pink and allow the clear interpretation of the test result. **If background color appears and interferes with interpretation of the test result, the result is considered invalid.** Should this occur, review the procedure and repeat the test with a new Test Strip.

External Quality Control
External controls may also be used to demonstrate that the reagents and assay procedure perform properly.

Quidel recommends that positive and negative controls be run every 25 tests, and as deemed necessary by your internal quality control procedures.

If the controls do not perform as expected, repeat the test or contact Quidel Technical Support before testing patient specimens.

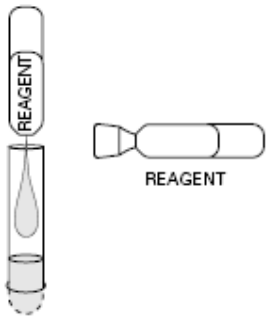
External positive and negative control swabs are supplied in the kit and should be tested using the Swab Procedure.

TEST PROCEDURES

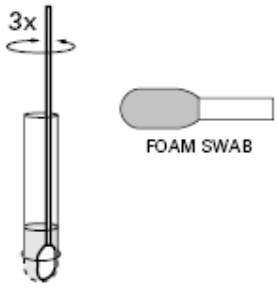
Expiration date: Check expiration on each individual test package (tray or outer box) before using. *Do not use any test past the expiration date on the label.*

Nasal Swab Procedure

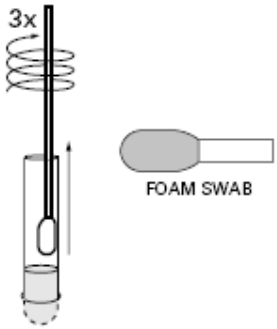
1. Dispense all of the Extraction Reagent Solution from the Reagent Tube. Gently swirl the Extraction Tube to dissolve its contents.



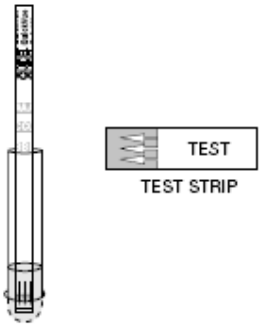
2. Place the patient swab sample into the Extraction Tube. Roll the swab at least three (3) times while pressing the head against the bottom and side of the Extraction Tube.



3. Roll the swab head against the inside of the Extraction Tube as you remove it. Dispose of the used swab in accordance with your biohazard waste disposal protocol.



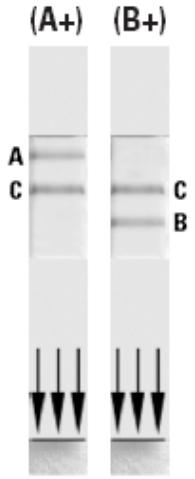
4. Place the Test Strip into the Extraction Tube with the arrows on the Test Strip pointing down. Do not handle or move the Test Strip until the test is complete and ready for reading.



5. Read result at ten (10) minutes. Some positive results may appear sooner.

INTERPRETATION OF RESULTS

Positive Result:
At ten minutes, **ANY** shade of a pink-to-red Test Line forms, either above or below the blue control line, **AND** the appearance of a blue procedural Control Line indicates a positive result for the presence of influenza A and/or B viral antigen.



Hold the test strip with the **arrows pointed down.**

- If the red line is **above** the Control Line, the test results are positive for type A. See image to right (A+).
- If the red line is **below** the Control Line, the test results are positive for type B. See image to right (B+).

Negative Result:
At ten minutes, the appearance of ONLY the blue procedural Control Line indicates the sample is negative for influenza A and B viral antigen. A negative result should be reported as a presumptive negative for the presence of influenza antigen.

Invalid Result:
If at ten minutes, the blue procedural Control Line does not appear, even if any shade of a pink-to-red Test Line appears, **the result is considered invalid.** If at ten minutes, the background color does not clear and it interferes with the reading of the test, the result is considered invalid. If the test is invalid, a new test should be performed with a new patient sample and a new Test Strip.

APPENDIX X

Binax NOW *Streptococcus pneumoniae* test

PRINCIPLES OF THE PROCEDURE

The Binax NOW® *Streptococcus pneumoniae* Test is an immunochromatographic membrane assay used to detect pneumococcal soluble antigen in human urine and CSF. Rabbit anti-*S. pneumoniae* antibody, the Sample Line, is adsorbed onto nitrocellulose membrane. Control antibody is adsorbed onto the same membrane as a second stripe. Both rabbit anti-*S. pneumoniae* and anti-species antibodies are conjugated to visualizing particles that are dried onto an inert fibrous support. The resulting conjugate pad and the striped membrane are combined to construct the test strip. This test strip and a well to hold the swab specimen are mounted on opposite sides of a hinged, book-shaped test device (U.S. patent No. 91/214051).

To perform the test (2 U.S. patents pending), a swab is dipped into the specimen (either urine or CSF), removed, and then inserted into the test device. Reagent A, a buffer solution, is added from a dropper bottle. The device is then closed, bringing the sample into contact with the test strip. Pneumococcal antigen present in the sample reacts to bind anti-*S. pneumoniae* conjugated antibody. The resulting antigen-conjugate complexes are captured by immobilized anti-*S. pneumoniae* antibody, forming the Sample Line. Immobilized control antibody captures anti-species conjugate, forming the Control Line.

Test results are interpreted by the presence or absence of visually detectable pink-to-purple colored lines. A positive test result, read in 15 minutes or less depending on the concentration of antigen present in the specimen, will include the detection of both a Sample and a Control Line. A negative test result, read in 15 minutes, will produce only a Control Line, indicating that *S. pneumoniae* antigen was not detected in the sample. Failure of the Control Line to appear, whether the Sample Line is present or not, indicates an invalid assay.

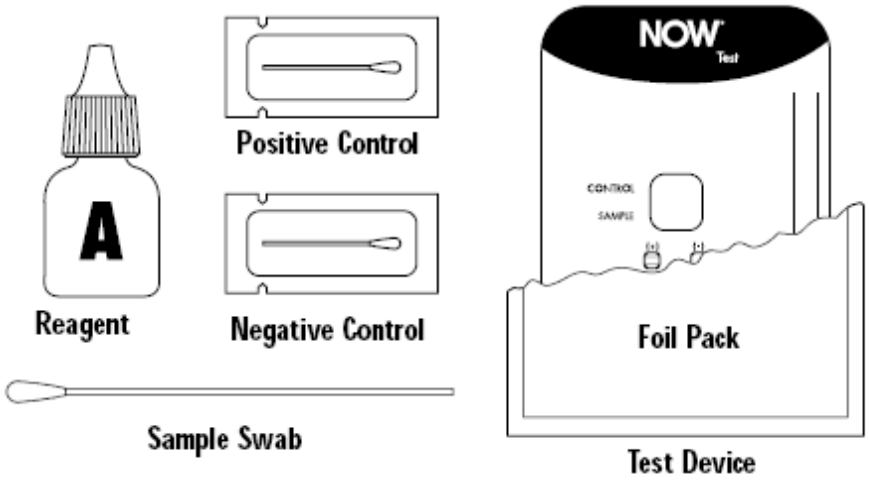
REAGENTS AND MATERIALS

Materials Provided

ITEM	DESCRIPTION
Test Devices	A membrane coated with rabbit antibody specific for *S. pneumoniae* antigen and with control antibody is combined with rabbit anti-*S. pneumoniae* antigen and anti-species conjugates in a hinged test device.
Reagent A	Citrate / Phosphate buffer with sodium lauryl sulfate, Tween 20, and sodium azide.
Sample Swabs	Designed for use in the Binax NOW® *Streptococcus pneumoniae* Test. **Do not use other swabs.**

APPENDIX X

Sample Swabs	Designed for use in the Binax NOW® *Streptococcus pneumoniae* Test. **Do not use other swabs.**
Positive Control Swab	Heat inactivated *S. pneumoniae* dried onto swab.
Negative Control Swab	*S. pneumoniae* negative swab.



Materials Not Provided

clock, timer, or stopwatch; standard urine collection containers, or CSF transport tubes

Accessory Item

Binax NOW® *Streptococcus pneumoniae* Test Control Swab Pack (catalog number 710-010) containing 5 positive and 5 negative control swabs.

PRECAUTIONS

1. INVALID RESULTS, indicated by no Control Line, can occur when an insufficient volume of Reagent A is added to the test device. To insure delivery of an adequate volume, hold vial vertically, ½ - 1 inch above the swab well, and slowly add free falling drops.
2. For *in vitro* diagnostic use.
3. The test device is sealed in a protective foil pouch. Do not use if pouch is damaged or open. Remove test device from pouch just prior to use. Do not touch the reaction area of the test device.
4. Do not use kit past its expiration date.
5. Do not mix components from different kit lots.
6. Swabs in the kit are approved for use in the Binax NOW® test. **Do not use other swabs.**
7. Solutions used to make the control swabs are inactivated using standard methods. However, patient samples, controls, and test devices should be handled as though they could transmit disease. Observe established precautions against microbial hazards.

8. Clean catch urine is not necessary for the NOW® test. Therefore, urine specimens used for this test may not be appropriate for bacteriological culture.
9. Once the Binax swab is dipped into CSF specimen, the sample is no longer sterile and may not be appropriate for culture. If CSF specimen will be cultured, either perform culture first or split CSF sample.

STORAGE AND STABILITY

Store kit at room temperature (59-86°F, 15-30°C). The Binax NOW® *Streptococcus pneumoniae* Test kit and reagents are stable until the expiration dates marked on their outer packaging and containers. Do not use the kit beyond its labeled expiration date.

59-86°F
15-30°C
STORAGE
TEMPERATURE

SPECIMEN COLLECTION

Allow all specimens to equilibrate to room temperature (59-86˚F, 15-30˚C) before testing in the Binax NOW® *Streptococcus pneumoniae* Test. Just before testing, mix specimen by swirling gently.

URINE (for diagnosis of pneumonia)
Collect urine specimens in standard containers. Store at room temperature (59-86˚F, 15-30˚C) if assayed within 24 hours of collection. Alternatively, store urine at 2-8˚C or frozen for up to 14 days before testing. Boric acid may be used as a preservative.

When necessary, ship urine specimens in leakproof containers at 2-8˚C or frozen.

QUALITY CONTROL

Daily Quality Control:
The Binax NOW® *Streptococcus pneumoniae* Test contains built-in positive and negative procedural controls. The manufacturer's minimum recommendation for daily quality control is to document these procedural controls for the first sample tested each day.

Positive Procedural Control
The pink-to-purple line at the "Control" position can be considered an internal positive procedural control. If capillary flow has occurred and the functional integrity of the device was maintained, this line will always appear.

Negative Procedural Control
The clearing of background color in the result window provides a negative background control. The background color in the window should be light pink to white within 15 minutes and should not interfere with the reading of the test result.

External Positive and Negative Controls:

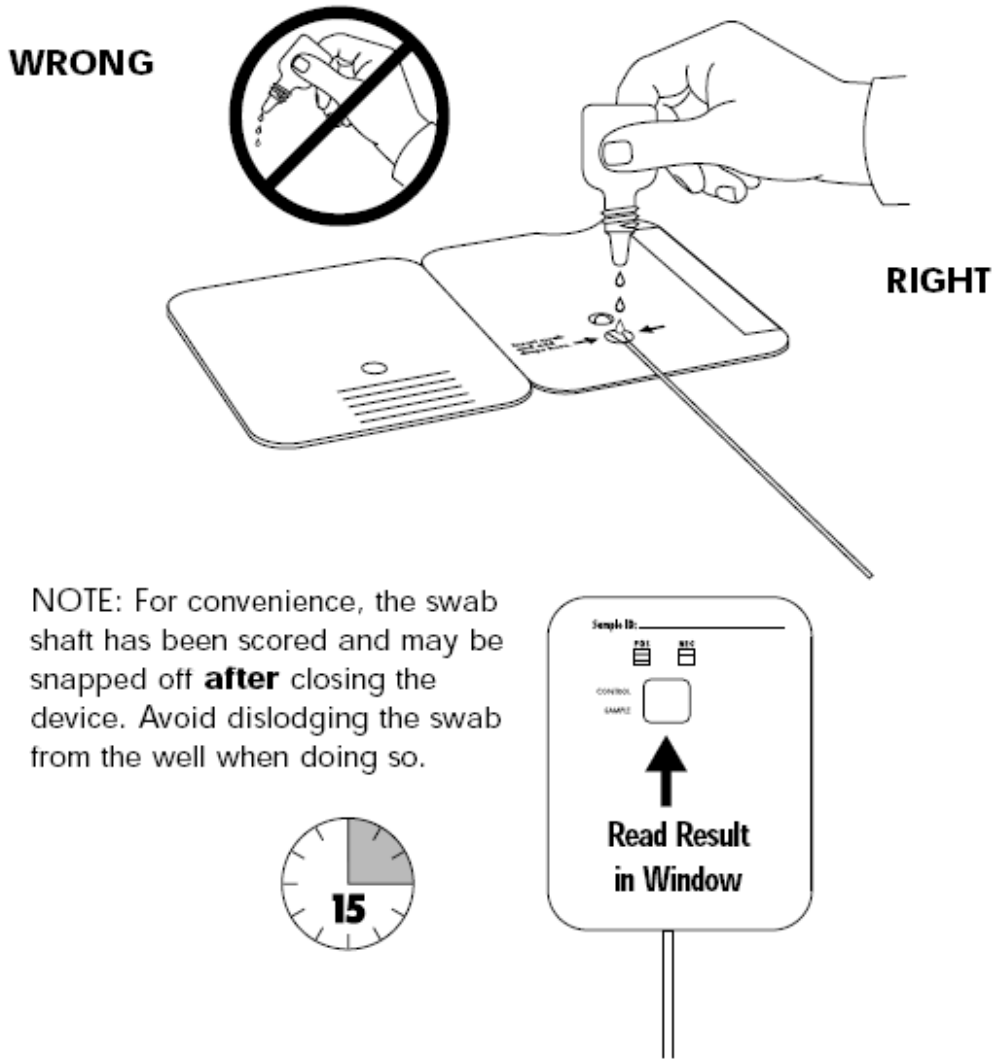
Good laboratory practice recommends the use of positive and negative controls to assure functionality of reagents and proper performance of assay procedure. Positive Control Swabs and Negative Control Swabs that will monitor the entire assay are provided in the test kits and should be tested using the Control Swab procedure. Controls should be tested once with each test kit opened, and as otherwise required by your laboratory's standard Quality Control procedures. Additional controls may be tested according to the requirements of local, state and/or federal regulations or of accrediting organizations.

If expected control results are not obtained, do not report patient results. Review the procedure and repeat control testing or contact Binax Technical Service by phone at **1-800-323-3199** or **1-207-772-3988**, or by facsimile at **1-207-761-2074**.

ASSAY PROCEDURE
Urine Samples, CSF Samples and Liquid Controls

Use a **URINE** sample when testing for **PNEUMOCOCCAL PNEUMONIA** and a **CSF** sample when testing for **PNEUMOCOCCAL MENINGITIS**.

1. Bring patient sample(s) and/or liquid control(s) to room temperature (59-86˚F, 15-30˚C), then swirl gently to mix. Remove device from its pouch **just before use** and lay flat.
2. Dip a Binax swab into the sample to be tested, completely covering the swab head. If the swab drips, touch swab to side of collection container to remove excess liquid.
3. There are two holes on the inner right panel of the device. Insert swab into the **BOTTOM** hole (swab well). Firmly push upwards so that the swab tip is fully visible in the top hole. **DO NOT REMOVE SWAB**.
4. Hold Reagent A vial vertically, ½ to 1 inch above the device. Slowly add three (3) free falling drops of Reagent A to the **BOTTOM** hole.
5. Immediately peel off adhesive liner from the right edge of the test device. Close and securely seal the device. Read result in window 15 minutes after closing the device. Results read beyond 15 minutes may be inaccurate. However, some positive patients may produce a visible sample line in less than 15 minutes.



ASSAY PROCEDURE
Binax NOW® Swab Controls

1. Remove device from the pouch **just before use**. Lay device flat.
2. There are two holes on the inner right panel of the device. Insert swab into the **BOTTOM** hole. Firmly push upwards so that the swab tip is fully visible in the top hole. **DO NOT REMOVE SWAB**.
3. Hold Reagent A vial vertically, ½ to 1 inch above the device. Slowly add six (6) free falling drops of Reagent A to the **BOTTOM** hole.
4. Immediately peel off adhesive liner from the right edge of the test device. Close and securely seal the device. Read result in window 15 minutes after closing the device. Results read beyond 15 minutes may be inaccurate. However, the Positive Control Swab sample line may be visible in less than 15 minutes.

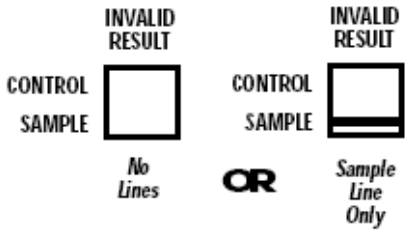
APPENDIX X

INTERPRETATION OF RESULTS

A **negative sample** will give a single pink-to-purple colored Control Line in the top half of the window, indicating a presumptive negative result. This Control Line means that the detection part of the test was done correctly, but no *S. pneumoniae* antigen was detected.

A **positive sample** will give two pink-to-purple colored lines. This means that antigen was detected. Specimens with low levels of antigen may give a faint patient line. **Any visible line is positive.**

If no lines are seen, or if just the Sample Line is seen, the assay is **invalid**. Invalid tests should be repeated. Call Binax Technical Service at (800) 323-3199 or (207) 772-3988 if the problem persists.



REPORTING OF RESULTS

Result	Recommended Report
Positive Urine	Positive for pneumococcal pneumonia.
Negative Urine	Presumptive negative for pneumococcal pneumonia, suggesting no current or recent pneumococcal infection. Infection due to *S. pneumoniae* cannot be ruled out since the antigen present in the sample may be below the detection limit of the test.
Positive CSF	Positive for pneumococcal meningitis.
Negative CSF	Presumptive negative for pneumococcal meningitis. Infection due to *S. pneumoniae* cannot be ruled out since the antigen present in the sample may be below the detection limit of the test.

REPORTING OF RESULTS

Result	Recommended Report
Positive Urine	Positive for pneumococcal pneumonia.
Negative Urine	Presumptive negative for pneumococcal pneumonia, suggesting no current or recent pneumococcal infection. Infection due to *S. pneumoniae* cannot be ruled out since the antigen present in the sample may be below the detection limit of the test.
Positive CSF	Positive for pneumococcal meningitis.
Negative CSF	Presumptive negative for pneumococcal meningitis. Infection due to *S. pneumoniae* cannot be ruled out since the antigen present in the sample may be below the detection limit of the test.

LIMITATIONS

The Binax NOW® *Streptococcus pneumoniae* Test has been validated using urine and CSF samples only. Other samples (e.g. plasma or other body fluids) that may contain *S. pneumoniae* antigen have not been evaluated.

A negative Binax NOW® test does not exclude infection with *S. pneumoniae*. Therefore, the results of this test as well as culture results, serology or other antigen detection methods should be used in conjunction with clinical findings to make an accurate diagnosis.

The Binax NOW® *Streptococcus pneumoniae* Test has not been evaluated on patients taking antibiotics for greater than 24 hours or on patients who have recently completed an antibiotic regimen. The effects of over-the-counter drugs have not been determined on persons with pneumococcal meningitis.

Streptococcus pneumoniae vaccine may cause false positive results in urine in the Binax NOW® *Streptococcus pneumoniae* Test in the 48 hours following vaccination. The effect of vaccination has not been determined on persons with pneumococcal meningitis. Hence, it is recommended that the Binax NOW® *Streptococcus pneumoniae* Test not be administered within 5 days of receiving the *S. pneumoniae* vaccine.

The accuracy of the Binax NOW® test in urine has not been proven in young children. Performance on CSF in young children, on the other hand, is established (see Performance Data - CSF).

CLINICAL SENSITIVITY AND SPECIFICITY (Retrospective Study)

As part of the retrospective study, urine specimens from 35 blood culture positive pneumococcal pneumonia patients and 338 presumed *S. pneumoniae* negative patients (373 total patients) were collected at 3 different facilities and evaluated in the Binax NOW® test. Binax NOW® test performance was calculated using standard methods. Sensitivity was 86%, specificity was 94%, and overall accuracy was 93%. Ninety-five percent (95%) confidence intervals are listed below.

	Blood Culture +	Blood Culture −
NOW® +	30	21
Result −	5	317

Sensitivity	**=**	**86%**	(71% - 94%)
Specificity	**=**	**94%**	(91% - 96%)
Accuracy	**=**	**93%**	(90% - 95%)

CLINICAL SENSITIVITY AND SPECIFICITY (Prospective Study)

In a separate seven-center prospective study, the Binax NOW® test was used to evaluate urine specimens collected from 215 hospitalized and outpatients presenting with lower respiratory symptoms or sepsis and from patients otherwise suspected of pneumococcal pneumonia. Patients were considered positive for pneumococcal pneumonia if diagnosed by positive blood culture.

The Binax NOW® test performed equivalently on both outpatients and hospitalized patients. Ninety-five percent (95%) confidence intervals are listed below.

Outpatient Performance

	Blood Culture +	Blood Culture −			
NOW® +	19	25	**Sensitivity**	**= 90%**	(70% - 97%)
Result −	2	90	**Specificity**	**= 78%**	(70% - 85%)
			Accuracy	**= 80%**	(72% - 86%)

Hospitalized Patient Performance

	Blood Culture +	Blood Culture −			
NOW® +	9	20	**Sensitivity**	**= 90%**	(60% - 98%)
Result −	1	49	**Specificity**	**= 71%**	(59% - 80%)
			Accuracy	**= 73%**	(62% - 82%)

CROSS-REACTIVITY

Urine Testing

Two hundred seventy (270) different organisms were isolated from the 338 negative patients tested as part of the above retrospective study. Of the 165 organisms isolated from patients with urinary tract infections, 15 (9%) produced positive results. These were 2/2 *Enterobacter cloacae*, 1/2 *Staphylococcus aureus*, 1/1 *Streptococcus* (non A,B), 1/1 *Streptococcus* (non D), 1/17 *Streptococcus* (Group D), 1/3 *Providencia stuartii*, 5/78 *Escherichia coli* and 3 with no identified pathogen. Of the 59 organisms isolated from patients with pneumonia, 3 (5%) were positive, including 1/3 *Mycobacterium kansasii* and 2/15 *Mycobacterium tuberculosis*. One of the 41 (2%) organisms isolated from bacteremic patients, *Proteus mirabilis*, was positive. There was no cross-reactivity with the 5 empyema isolates. Lastly, 4/100 urine specimens collected from people with no known infection were positive.

Due to the retrospective nature of this study, only a limited number of patients with each infection were available for testing and the complete clinical history of each is not known. Therefore, the presence of *S. pneumoniae* co-infection cannot be ruled out. When tested in pure culture (data below), these organisms do not cross-react in the NOW® test.