NETSCC, HTA

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Evaluation of droplet dispersion during non-invasive ventilation, oxygen therapy and nebulised drug delivery in clinical practice

Project Management Members

1. Chief Investigator: Dr Anita K Simonds, Academic Dept Sleep & Breathing, Royal Brompton Hospital, Sydney Street, London SW3 6NP 020 73518911

2. Co-investigators: Dr R Dickinson & Dr J Siggers , Bioengineering Dept, IC, Dr Michelle Chatwin & Dr Anne Hall RBH, Dr M Morrell, IC,

3. Statistician: Mr Winston Banya

4. Project Manager Dr Michelle Chatwin 020 73518911

5. Key Contact Dr A K Simonds (A.Simonds@rbht.nhs.uk)

Funder

NIHR HTA

Sponsor

Royal Brompton & Harefield NHS Foundation Trust
Contact : Wendy Butcher, R&D Dept, Royal Brompton Hospital

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1. INTRODUCTION

1.1 BACKGROUND

Influenza viruses are spread by droplets, but aerosols may be implicated. While many patients recover without serious illness, some with H1N1 swine flu will develop pneumonia/respiratory insufficiency requiring treatment by oxygen therapy (O2), ventilatory support or nebulised drugs, and this is more likely in those with underlying respiratory or cardiac disorders eg. chronic obstructive pulmonary disease (COPD), asthma, cystic fibrosis, genetic susceptibility, pregnancy or if the virus mutates. These therapies may generate droplets or aerosol during delivery which in the SARS outbreak was associated with an increased incidence of infection in healthcare workers (Fowler R et al 2004) and super spreading events on hospital wards (Yu I et al, 2007). Non-invasive ventilation (NIV) is unlikely to be effective in patients with overwhelming acute lung injury, but in early pneumonia and in those in whom influenza has caused an exacerbation of COPD or heart failure NIV may be effective in reducing the need for Intensive Care Unit (ICU) admission. Currently use of NIV in pandemic flu is controversial. Dept Health Pandemic Influenza guidance recommends NIV should be used with full infection control (aerosol generating) precautions by experienced units employing practice guidelines which have been developed by our team (Simonds, 2007), but there is no substantive evidence base, and NIV use is not advocated in other national guidelines. Hui et al (2006) carried out studies of NIV droplet distribution using a patient simulator and smoke particles but there have been no systematic studies in humans or during oxygen and nebuliser therapy, or physiotherapy.

1.2 RATIONALE FOR CURRENT STUDY

This research should provide the first analysis of droplet distribution around respiratory therapies in clinical circumstances which are relevant to H1N1 infection. Although the patients with chronic respiratory disease will not specifically have an exacerbation triggered by H1N1 influenza in this study, the results should be representative of any acute exacerbation and we will also study those with coryzal symptoms, some of whom may have H1N1 infection. The findings should enable healthcare professionals to understand patterns of geographical disutribution of respirable droplets whan caring for patients, inform selection of circuitry and interfaces to reduce dissemination, and by modelling the profile of decay of particles after therapy we hope to guide healthcare workers entry into rooms in stable patients.

Impact on practice: As this is the first analysis of distribution of droplets during NIV, O2 and nebuliser therapy in representative clinical circumstances, the results obtained should influence clinical practice and policy immediately by:
1) Informing the choice of interface/delivery systems
2) Guide health care workers to safer application in pandemic flu and enable them to understand relative risks.
3) Reduce the risk of dissemination to other patients and staff in superspreading events
4) Wider, safe use of NIV may reduce Intensive Care Unit (ICU) bed pressures, as NIV may be performed in respiratory ward areas/high dependency single rooms.

2. STUDY OBJECTIVES

The key objective is to understand the characteristics of droplet and aerosol dispersion around delivery systems during non-invasive ventilation (NIV), oxygen (O2) therapy, nebuliser therapy and physiotherapy procedures.
We will examine:
i) droplet size and count
ii) geographical distribution of droplets
iii) rise and decay of droplets over time after the therapies are initiated and discontinued
iv) the impact of modifications to the delivery system to reduce droplet/aerosol dissemination in A) normal subjects B) individuals with coryzal symptoms and C) patients with an acute exacerbation of chronic lung disease

2.1 PRIMARY OBJECTIVE/S

To evaluate the characteristics of droplets and aerosol generated using non-invasive ventilation, oxygen therapy, nebuliser use and physiotherapy in clinical practice.

2.2 SECONDARY OBJECTIVE/S

To determine whether particular delivery methods/interfaces generate more droplets.

To establish how can droplet characteristic information be applied to inform safe use of these therapies in patients with H1N1 swine flu, and other droplet/aerosol borne diseases.

3. STUDY METHODOLOGY

3.1 OVERALL DESIGN

This is an observational study with subjects and patients acting as their own control

3.2 SETTING AND TIMESCALE

The study will be carried out in a single centre (Royal Brompton Hospital) over four months (Sept – Dec 09)

3.3 STUDY OUTCOME MEASURES

Number of droplets in size range 0.3-10 microns measured during conditions listed below.

3.4 SPECIFIC METHODS

DROPLET COUNT AND SIZING:
We will count droplets in size range 0.3 to 10.0 µm within distributions 0.3-0.5, 0.5-1.0, 1.0-3.0,3.0-5.0, 5.0-10.0 and >10µm using Aerotrak Model 8220 optical particle counter with counting efficiency 50% +/- 10% at 0.3 µm and 100% +/- 10% at 0.45 µm and greater. We will examine dissemination of smaller droplet (aerosol) size using a P-Trak Ultrafine Condensation particle counter (particle size range 0.02 to 1.0µm) at sample flow rate 100 cm^3/min. Each sampling will be carried out twice over 10 seconds, on 3 occasions at sampling points: 1) adjacent (within 2 cm) to mouth or mask 2) 0.5m from mouth or mask 3) 1m from mouth or mask and 4) 3m from mouth or mask with sampling points 2)-4) being carried out in radial positions 2 laterally to subject/patient, 1 directly in front of subject/patient and 1 above subject. The Aerotrack and P-Trak counter devices will be mounted on tripods to maintain accuracy and reproducibility of measurements.

Mathematical modelling: We will use mathematical modelling of droplet motion and dispersion to derive the expected droplet distribution at different distances. Fitting the model with observations at a number of positions will allow interpolation and extrapolation of the measured droplet distribution as a function of size of the droplet and distance from the patient/mask/interface, for a range of room conditions. In turn this will enable us to predict the safe times and distances beyond which exposure can be considered comparable to spontaneous breathing or negligible.

3.5 PARTICIPANTS

Groups

We will study 3 groups: normal subjects, subjects with coryzal (Common cold or flu-like) symptoms and adult patients with chronic lung disorders.

Inclusion criteria

Normal subjects: Age 18 years and above. Able to speak English and understand protocol.

Coryzal subjects: Age 18 years and above. Have 2 of any of following - raised temperature or history of raised temperature, sore throat, headache, muscle aches and pains, cough in previous 24-48 hours. Arterial oxygn saturation 95% or above on air.

Patients:
A clinical diagnosis confirmed by medical consultant of COPD, asthma, cystic fibrosis, bronchiectasis, chest wall disorder or neuromuscular disease eg. Duchenne muscular dystrophy.
Admitted with infective exacerbation defined by increased breathlessness, raised white cell count or temperature or CRP (C-reactive protein - raise values indicate infection or inflammation).
Requiring treatment with oxygen therapy and non-invasive ventilation as clinically indicated.

Exclusion criteria

Normal subjects: Current illness or underlying chronic condition. Pneumothorax in previous 3 months. Unable to understand English or trial information.

Coryzal subjects: Underlying chronic condition. Arterial oxygen saturation <95% on air. Pneumothorax in previous 3 months. Unable to understand English or trial information.

Patients: Hamodynamically unstable (systolic blood pressure <90 mmHg, uncontrolled arrhythmia), medically unstable, arterial oxygen tension (PaO2)<7.5 kPa on O2 or NIV, arterial carbon dioxide tension (PaCO2)>7.5 kPa on NIV or O2, unable to breathe spontaneously for <4 hours. Unable to understand English or trial information.

Sampling method

Normal subjects will be recruited from departmental database of normal subjects who have participated in previous studies.
Coryzal subjects will be recruited from Occupational Health dept, and staff who develop symptoms while on duty.
Patients will be recruited from those already inpatients on respiratory ward with an acute infective exacerbation of chronic lung disease. At any one time we have around 15-20 patients on the ward receiving oxygen therapy/non-invasive ventilation. The research team are either members of the clinical team or interact with the team on a daily basis.

Sample size

Background
It should be stressed that this work is almost exclusively exploratory in nature. This is because there are very many unknowns. It is not known whether the material generated by infected individuals breathing, coughing or undergoing interventions is in the form of a fine aerosol or larger droplets[1]. Non-invasive ventilation and nebulisation have been termed 'potential aerosol generating procedures' but this is based on presumption not evidence. In the Department of Health Pandemic Flu guidelines[2] it is stipulated that high efficiency masks should be used when working within 1 metre of the patient and that beds of patients being cohort nursed should be more than 1m apart. There is little primary evidence for either of these stipulations but in the SARS outbreak superspreading events (ie. at least 3 cases arising from one index case) were associated with a distance between beds <1 m and index cases with the use of oxygen therapy or non-invasive ventilation[3].
Further, the 'dose' needed to infect is not clear as droplets are a proxy measure of virus presence/infectivity, and sicker patients with higher viral loads are likely to need more therapeutic interventions.
Moreover we do not know the rate of decay of droplets over time after interventions have been discontinued. Again this will be partly related to size as larger droplets with greater mass will more quickly fall to the floor or onto bedding.

Droplet size and number; pilot data, variability and clinically meaningful difference.
We have pilot data from 5 normal subjects sampled at the mouth or mask and in one droplet size range (5-10 microns). This size range is known as the 'respirable range' representing droplets likely to be deposited in lungs; larger droplets are not inspired and very small aerosol particles do not have sufficient mass to drop out in lung and are expired as easily as they are inspired. Droplets generated by interventions (oxygen therapy, non-invasive ventilation etc) should be compared to those generated by the subject/patients breathing spontaneously as a baseline of zero droplets is not clinically realistic. We are therefore carrying out comparisons with spontaneous breathing with each subject/patient acting as their own control.

Our pilot data above estimated a droplet count of 900 (sd=100) with spontaneous breathing.

In the absence of any other published information and the uncertainties outlined above, we have chosen a doubling in this droplet count to represent a significant increase in risk of spread to healthcare staff or other patients. This estimate is informed by the observation that coughing and

sneezing in pilot work resulted in a count of around 1800; and that coughing and sneezing increase the risk of infection.

We used Statistical Analysis Systems (SAS) version 9.1 to estimate the required study group sizes.

Using our pilot estimates and a false-positive rate (α) of 0.05, calculations for a single two-group comparison with 80% power indicate that very small groups would be required.

We have, however, increased our group sizes to account for:
the possibility that variability may be higher in patients (currently unknown);
and the four comparisons that are to be undertaken.
Sample sizes are therefore normal subjects 10, coryzal subjects 10, patients 20

This model is based on droplet counts in one size range at the mouth and is suitable for our primary purpose. Again, with the lack of any information from elsewhere, we do not know whether our sample size will be sufficient for our other questions: eg number of droplets at different distances from patient or the decay over time. Initial findings will provide further information. If variability estimates are greater or differences smaller compared to spontaneous breathing, further recruitment will be possible.

Statistical advice was provided by Mr Winston Banya, Senior Statistician, R&D Dept Royal Brompton Hospital

Pre-registration evaluations

We will check arterial oxygen saturation level in normal subjects and subjects with coryzal symptoms using an oximeter ear probe is 95% or above. In coryzal subjects we will carry out nasopharyngeal aspirate and throat and nasal for virology examination. Virology results will not be known till after study tests are done, so will inform analysis but not needed for entry as symptoms alone determine eligibility.

Patients will have a arterial oxygen saturation value of more than 88% and transcutaneous carbon dioxide value of less than 7.5kPa on oxygen therapy and or non-invasive ventilation.

Withdrawal criteria

The trial will be discontinued if the Chief Investigator
feels it is unsafe to continue. As the therapies used are in routine clinical practice in patients and researchers are members of the clinical team and routinely apply these therapies in patients, including those in first wave of swine flu, this risk is relatively low.

3.6 RECRUITMENT AND METHODLOGICAL PROCESS

Recruitment
Recruitment will take part at Royal Brompton Hospital. Normal subjects will be recruited from departmental database and volunteers working in the hospital. Coryzak subjects will be recruited from Occupational Health and from individuals working in the hospital who develop symptoms while on duty

Written informed consent will be obtained by the research fellow, Dr Michelle Chatwin or CI at Royal Brompton Hospital whi have all had training in obtaining consent. Subjects and patients will be provided with Information sheets. Normal subjects and patients will have 24 hours to decide whether to participate and coryzal subjects will have 1 hour to decide.

Methodological process

Description: This is an observational trial which will be carried out in a single hospital side room on respiratory ward at Royal Brompton Hospital. The aim is to measure the size and number of droplets and smaller (aerosol) particles generated during treatment with non-invasive ventilation, oxygen therapy, nebuliser therapy and during physiotherapy.

Three groups will take part: A)normal subjects, B)subjects with coryzal (common cold or flu-like) symptoms, and C)patients with respiratory insufficiency due to chronic obstructive pulmonary disease (COPD), cystic fibrosis, chronic asthma, bronchiectasis, neuromuscular disease receiving NIV/O2/nebuliser therapy as indicated for an infective exacerbation. Each subject or patient will take part on one occasion, the study taking approximately 3 hours to complete

Subjects and patients:
A) Normal subjects: will be recruited from our database of normals (aged 18 years and above) and above. Exclusions: no current illness or underlying chronic condition.

B) Individuals with common cold or flu like (coryzal) symptoms defined by pyrexia, and 2 of sore throat, muscle aches and pains, headache, cough within previous 24-48 hours (age 18 yrs and above) will be recruited from contacts from normal patient database, Occupational health dept RBH and from staff developing symptoms while on duty. They will be studied after having nasopharyngeal aspirate and swabs to confirm diagnosis using aerosol generating PPE precautions. Exclusion criteria: no underlying chronic health conditions, medically stable.

C) Patients with chronic respiratory failure will be recruited from those admitted to ward with as infective exacerbation of chronic respiratory disease.
Inclusion criteria: those with chronic obstructive pulmonary disease (COPD), cystic fibrosis, bronchiectasis, chest wall disorder and neuromuscular disease). These groups are selected as willl contain older patients with COPD and younger patients with cystic fibrosis and eg. Duchenne muscular dystrophy) in whom non-invasive ventilation and Oxygen therapy is clinically indicated.
Exclusion criteria: Haemodynamically or medically unstable, PaO2 <7.5 kPa, PaCO2 >7.5 kPa pH <7.34 on therapy, cognitive inability to able to understand study information sheet, able to breathe spontaneously for < 4 hours

Technologies being assessed: Non-invasive ventilation using standard bilevel pressure support device using a range of interfaces and settings, nasal continuous positive airway pressure (CPAP) therapy, oxygen (O2) therapy via 60%, 35% and 24% masks

Measurements: droplets will be visualised using a Model 8220 Aerotrak Optical particle counter (TSI Inc.) with particle size detection 0.3-10 microns, and a Model 8525 P-Trak Ultrafine Condensation particle counter (TSI Inc) adjacent to subject/delivery system, 1 m from delivery system and 3 m from patient/subject at 6 fixed radial points.

Investigation plan

On arrival in side room subjects and patients will be assessed breathing spontaneously at rest, during simulated coughing and then when receiving non-invasive ventilation and oxygen therapy, physiotherapy and nebulised saline therapy in random order

Droplet distribution will be measured in following test conditions (selected as clinically representative):
For A) Normal subjects and B) Subjects with coryzal symptoms

i) Control: spontaneous breathing and simulated cough with and without surgical mask which will take approx 10 minutes.
ii) Non-invasive ventilation: A bilevel ventilator will be used: in random order delivery with non vented fullfacemask, Total facemask and helmet with and without filter modification and vented fullfacemask. Ventilator settings: Inspiratory positive airway pressure (IPAP) Expiratory airway pressure (EPAP) IPAP/EPAP 20/5 15/5 10/5 cmH2O. Continuous positive airway pressure (CPAP) 5 and 10 cmH2O. This will take approx 1 hour
iii) Oxygen therapy will be delivered using 60%, 35%, 24% masks. This will take approx 30 mins. This will take about 20 minutes
iv) nebulised 0.9% saline delivered from standard nebuliser. This will take 10 minutes.
v) Standardised physiotherapy. This will take 10 minutes.

Subjects will be able to have rest periods between the runs as we will be sampling the room to ensure control conditions obtain and get background counts.

C) Patients with respiratory insufficiency:

(I) Spontaneous breathing and during simulated cough. This will take approximately 10 minues)
(II) Non-invasive ventilation: using current clinically indicated NIV settings deovered in random order through non-vented fullfacemask, Total facemask, helmet with and without filter modification and vented mask. This will take approximately 45 minutes.
(III) O2 therapy 24% ventimask spontaneously breathing. This will take approximately 5-10 minutes
IV) nebulised 0.9% saline delivered by standard nebuliser. This will take approximately 10 minutes.
(V)During physiotherapy using 24 % O2 mask (this will take about 10 minutes)
Patients will be monitored with arterial oxygen satuaration (SaO2), transcutaaeous carbon dioxide tension (TcCO2) and heart rate measurement using a non-invasive ear probe (Tosca) throughout (I) – (IV).

They will be able to have rest periods between the runs as we will be sampling the room to ensure control condition obtain and get background counts.

Droplet and aerosol characterisation:
We will count droplets in size range 0.3 to 10.0 µm within distributions 0.3-0.5, 0.5-1.0, 1.0-3.0,3.0-5.0, 5.0-10.0 and >10µm using Aerotrak Model 8220 optical particle counter with counting efficiency 50% +/- 10% at 0.3 µm and 100% +/- 10% at 0.45 µm and greater. We will examine dissemination of smaller droplet (aerosol) size using a P-Trak Ultrafine Condensation particle counter (particle size range 0.02 to 1.0µm) at sample flow rate 100 cm3/min. Each sampling will be carried out twice over 10 seconds, on 3 occasions at sampling points: 1) adjacent (within 2 cm) to mouth or mask 2) 0.5m from mouth or mask 3) 1m from mouth or mask and 4) 3m from mouth or mask with sampling points 2)-4) being carried out in radial positions 2 laterally to subject/patient, 1 directly in front of subject/patient and 1 above subject. The Aerotrack and P-Trak counter devices will be mounted on tripods to maintain accuracy and reproducibility of measurements.

Mathematical modelling: We will use mathematical modelling of droplet motion and dispersion to derive the expected droplet distribution at different distances. Fitting the model with observations at a number of positions will allow interpolation and extrapolation of the measured droplet distribution as a function of size of the droplet and distance from the patient/mask/interface, for a range of room conditions. In turn this will enable us to predict the safe times and distances beyond which exposure can be considered comparable to spontaneous breathing or negligible.

Equipment:
Non-invasive ventilation: we will use a Saime Elisee bilevel ventilator which can deliver a variety of inspiratory positive airway pressures (IPAP) and expiratory positive airway pressures (EPAP) and fixed level continuous positive airway pressure (CPAP) through a single limb and double limb circuit. The pressures of IPAP/EPAP 20/5, 15/5 and 10/5 cmH2O (spontaneous triggered mode) and CPAP 5

and 10 cmH2O have been selected as clinically representative. These pressures will be used in normal subjects and those with coryzal symptoms. In the patient group we will use the IPAP/EPAP settings and back-up respiratory rate as clinically indicated.

Interfaces: we will use a fullfacemasks (ResMed) non vented with filtered (intersurgical) exhalation port, and vented masks (ResMed), Total mask (Respironics/Philips) in all subjects and patients, and in 5 subjects a helmet (Rusch).

Oxygen therapy: 60% and 35% via high flow reservoir mask, 24% via Venturi mask in normal subjects and those with coryzal symptoms, 24% via Venturi mask in patients.

Physiotherapy: will be standardised as cycles of deep breathing, with percussion or shaking to loosen any secretions followed by an assisted cough initiated manually, augmented by a physiotherapist performing inward and upward pressure on the lower thorax to aid expectoration, after which the patient rests and cycle repeated as required. It will be performed by 1 physiotherapist (MC) who has perfomed standardised physiotherapy manoeuvres in other randomised crossover trials.

Nebuliser: Actineb nebuliser (Clement Clark) generating droplets 3-10 microns of 0.9% saline

Time line
Aug 1-31 Ethics application AS, Appoint fellow (likely secondment to speed onset of project)- run in period
Sept 1-15 training in measurements, equipment use, recruit normal subjects and coryzal subjects
Sept 15-Oct 15 Studies on normal subjects, coryzal subjects
Oct 15- Nov 30 Studies in respiratory insufficiency pts, creation and testing mathematical model. Further data collection if required.
Dec 1-31 Data analysis, write-up, further plans

There will be an interim analysis and mathematical modelling after 10 subjects and 10 patients have been studied.

Non-invasive ventilation, Oxygen therapy, nebuliser therapy and standardised physiotherapy will be delivered by research fellow and Dr Michelle Chatwin.

4. ETHICAL CONSIDERATIONS

The main risk is to research staff in dissemination of H1N1 of other coryzal virus. Full personal protective equipment will be used and the research team members are fully familiar with this and have experience in managing H1N1 patients. Some team members have already had swine flu themselves so will be immune.

There is a very small risk of a subject or patient using non-invasive ventilation (NIV) developing a pneumothorax. The patients already will be using NIV as part of their clinical management.

5. ADVERSE EVENTS

Potential adverse events:

1. Research team member becoming infected with swine flu.
   The individual would be with drawn from doing the project and treated with Oseltamivir in normal way. In practice it will be difficult to establish if the individual was infected durig the study or by contact with other infected patients or from contact from within or outside the hospital

All adverse events will be reported. Depending on the nature of the event the reporting procedures below will be followed. Any questions concerning adverse event reporting will be directed to the Chief Investigator in the first instance.

Non-serious AEs
All such events, whether expected or not, will be recorded.

Serious AEs
An SAE form should be completed and faxed to the Chief Investigator within 24 hours. However, hospitalisations for elective treatment of a pre-existing condition will not be reported as SAEs.

All SAEs will be reported to the REC overseeing the research and the research sponsor, where in the opinion of the Chief Investigator, the event was:

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs will be submitted within 15 days of the Chief Investigator becoming aware of the event, using the COREC SAE form for non-IMP studies.

Investigators will report any SAEs as required by their Local Research Ethics Committee and/or Research & Development Office.

6. ASSESSMENT AND FOLLOW-UP

We do not plan to follow-up patients after the study. Virology results will be fed back to coryzal subjects and appropriate action advised.

7. STATISTICS AND DATA ANALYSIS

Data will by analysed using ANOVA with correction for repeated measure. Satistical advice will be provided by Mr Winston Banya, R&D Dept, Royal Brompton & Harefield NHS Foundation Trust.

Data and all appropriate documentation will be stored for a minimum of 5 years after the completion of the study, including the follow-up period.

8. REGULATORY ISSUES

8.1 ETHICS APPROVAL

The Chief Investigator will obtain ethical approval from a Research Ethics Committee via the IRAS system. The study will not commence until ethical approval is obtained and will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.2 CONSENT

Consent to enter the study will be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent will be obtained. The right of the participant to refuse to participate without giving reasons will be respected. All participants are free to withdraw at any time from the research without giving reasons

and without prejudicing further treatment. Consent will be obtained by the patients existing clinical consultant.

8.3 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study in line with the Data Protection Act 1998.

8.4 INDEMNITY:

NHS INDEMNITY COVER

8.5 SPONSOR

Royal Brompton & Harefield NHS Foundation Trust

8.6 FUNDING & COSTS

NIHR HTA will fund this study. Travel cost to £20 are available to normal and coryzal subjects.

8.7 AUDITS AND INSPECTIONS

Sponsor and other regulatory bodies will ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

9. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through by Dr Michelle Chatwin (M.Chatwin@rbht.nhs.uk)

10. PUBLICATION POLICY

Results from this research will be reported and disseminated via peer reviewed journals and via conference presentations. No personal or identifiable data will be present in any public reports of this research.

11. REFERENCES

1. Tellier R. Review of aerosol transmission of influenza A virus. *Emerg Infect Dis* 2006;**12**:1657-62.

2. Fabian P, McDevitt JJ, DeHaan WH, Fung ROP, Cowling BJ, Chan KH *et al*. Influenza virus in human exhaled breath: an observational study. *PLoS One* 2008;**3**:e2691.

3. Department of Health. Pandemic Influenza: Guidance for infection control in critical care. 2008.

4. Simonds AK,.Sokol DK. Lives on the line? Ethics and practicalities of duty of care in pandemics and disasters. *Eur Respir J* 2009;1-7.

5. Department of Health. Pandemic Flu. Managing demand and capacity in health care organisations (Surge). 2009.

6. Gomersall CD, Tai DYHT, Derrick JL, Goh MS, Buckley TA, Chua C *et al*. Expanding ICU facilities in an epidemic: recommendations based on experience from SARS epidemic in Hong Kong and Singapore. *Intensive Care Medicine* 2006;**32**:1004-13.

7. Guidelines from the British Infection Society, British Thoracic Society and DH. Pandemic Flu:clinical management of patients with influenza-like illness during an influenza pandemic. *Thorax* 2007;**62**.

8. Levy M, Tanios MA, Nelson D, Short K, Senechia A, Vespia J *et al*. Outcomes of patients with do-not-intubate orders treated with noninvasive ventilation. *Crit Care Med* 2004;**32**:2002-7.

9. Fowler RA, Guest CB, Lapinsky SE, Sibbald WJ, Louie M, Tang P *et al*. Transmission of severe acute respiratory syndrome during intubation and mechanical ventilation. *Am J Respir Crit Care Med* 2004;**169**:1198-202.

10. Scales DC, Green K, Chan AK, Poutanen SM, Foster D, Nowak K *et al*. Illness in Intensive Care Staff after brief exposure to Severe Acute Respiratory Syndrome. *CDC* 2003;**9**.

11. Xiao Z, Li Y, Chen RC, et al. A retrospective study of 78 patients with severe acute respiratory syndrome. *Chin Med J* 2003;**116**:805-10.

12. Varia M, Wilson S, Sarwal S, McGeer A, Gournier E, Galanis E *et al*. Investigation of a nosocomial outbreak of severe acquired respiratory syndome (SARS) in Toronto, Canada. *CMAJ* 2003;**169**:285-92.

13. Cheung TMT, Yam LYC, So LKY, Lau ACW, Poon E, Kong BMH *et al*. Effectiveness of noninasive positive pressure ventilation in the treatment of acute respiratory failure in severe acute respiratory syndrome. *Chest* 2004;**126**:845-50.

14. Yam LYC, Chan AYF, Cheung TMT, Tsui ELH, Chan JCK, Wong VCW. Non invasive versus invasive mechanical ventilation for respiratory failure in severe acute respiratory syndrome. *Chin Med J* 2005;**118**:1413-21.

15. Yu IT, Li Y, Wong TW, Tam W, Chan AT, Lee JH *et al*. Evidence of airborne transmission of severe acute respiratory syndrome virus. *N Engl J Med* 2004;**350**:1731-9.

16. Hugonnet S,.Pittet D. Transmission of severe acute respiratory syndrome in critical care: do we need a change? *Am J Resp Crit Care Med* 2004;**169**:1177-8.

17. Seto WH, Tsang D, Yung RW, Ching TY, Ng TK, Ho M *et al*. Effectiveness of precautions against droplets and contact in prevention of nosocomial transmission of severe acute respiratory syndrome (SARS). *Lancet* 2003;**361**:1519-20.

18. Lau JTF, Fung KS, Wong TW, Kim JH, Wong E, Chung S *et al*. SARS transmission among hospital workers in Hong Kong. *Emerg Infect Dis* 2004;**10**:280-6.

19. Hui DS, Hall SD, Chan MTV, Chow BK, Tsou JY, Joynt GM *et al*. Noninvasive positive-pressure ventilation. An experimental model to assess air and particle dispersion. *Chest* 2006;**130**:730-40.

20. Somogyi R, Vesely AE, Azami T, Preiss D, Fisher J, Fowler RA. Dispersal of respiratory droplets with open vs closed oxygen delivery masks: implications for transmission of severe acure respiratory syndrome. *Chest* 2004;**125**:1157.

21. Mardimae A, Slessarev M, Han J, Sasano H, Sasano N, Azami T *et al*. Modified N95 mask delivers high inspired oxygen concentrations while effectively filtering aerosolized microparticles. *Ann Emerg Med* 2006;**48**:391-9.

22. Ip M, Tang JW, Hui DS, Wong ALN, Chan MTV, Joynt GM *et al*. Airflow and droplet spreading around oxygen masks: a simulation model for infection control research. *Am J Infect Control* 2007;**35**:684-9.

23. Keady PB. Getting data you need with particle measurements. *Indoor Environ Connect* 2000;**2**:1-5.

Appendix 1
Participant Consent Withdrawal Form

Royal Brompton & Harefield NHS
NHS Foundation Trust
Royal Brompton Hospital
Sydney Street
London SW3 6NP

Centre Number:
Study Number:
Patient Identification Number for this trial:

CONSENT WITHDRAWAL FORM

Title of Project: Evaluation of droplet dispersion during non-invasive ventilation, oxygen therapy and nebulised drug delivery in clinical practice

Name of Researcher:

Please initial box if you agree

1. I wish to withdraw from further participation in this trial ☐

   If you have withdrawn your participation in the treatment phase of this study, you have the option of participating in the post-treatment follow-up phase. However, if you DO NOT wish to take part in the follow-up, please complete the next section:
2. I wish to withdraw from further trial-related follow-up ☐

   Your participation in _____ means that we have already gathered some data. We would like to use this information in the future for analysing this trial and for future research. However, if you DO NOT wish this information to be used, please complete the following section:
3. I wish to withdraw consent to using any tissue samples* ☐
4. I wish to withdraw consent to using blood samples I have given* ☐

5. I wish to withdraw consent to using any data gathered prior to the date of this form ☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Person taking consent (if different from researcher)	Date	Signature
_____	_____	_____
Researcher	Date	Signature

When completed, 1 for patient; 1 for researcher site file; 1 (original) to be kept in medical notes

Appendix 2
LETTER TO PARTICIPANT GP

Royal Brompton & Harefield NHS
NHS Foundation Trust
Royal Brompton Hospital
Sydney Street
London SW3 6NP

GP LETTER

Evaluation of droplet dispersion during non-invasive ventilation, oxygen therapy and nebulised drug delivery in clinical practice

Dr <name>
<address>
<address>
<address>

<date>

Re: Patient Forename SURNAME, DOB, Address

Dear Dr <name>,

We are writing to inform you that your patient, has agreed to participate in the above research study at the Royal Brompton and Harefield NHS Foundation Trust. Your patient was enrolled into the study on **<date>**. We plan to recruit a total of 40 subjects and patients into the study. Patients attend on one occasion for about 3 hours. Approval for this study has been granted by <name of Research Ethics Committee>.

3 groups will be studied:

Group 1 Normal subjects

Group 2 Normal subjects with common cold or flu-like (coryzal) symptoms)

Group 3 Patient with an infective exacerbation of chronic lung disease being treated with oxygen therapy and non-invasive ventilation

In each group we will evaluate droplet distribution during oxygen therapy, non-invasive ventilation using a variety of interfaces and settings, nebuliser therapy and standard physiotherapy. Droplet or aerosol spread of infection to healthcare staff and other patients was implicated in the SARS outbreak and the aim of the study is to demonstrate which therapies produce more droplets and whether simple modifications can be introduced to reduce risk of dispersion and improve safety in H1N1 swine flu. Patients will receive therapies as clinically indicated and droplets will be measured using a handheld optical counter.

We may contact you to ask for information about significant medical events that may occur during the course of the study.

If you want any further details about the study, the involvement of your patient, or you wish to see a more detailed description of the study, please contact <name of local CI or trial coordinator>

Yours sincerely,

Dr Anita Simonds
Consultant in Respiratory Medicine
RoyalBrompton & Harefield NHS Foundation Trust
Sydney St,London SW3 6NP

Tel/fax 0207 351 8911
A.Simonds@rbht.nhs.uk