STUDY PROTOCOL

Expired Nitrous Oxide predicting ReADmission (NORAD) Study

STUDY TITLE

A prospective cohort study to evaluate fractional exhaled nitric oxide levels in hospitalised patients with acute exacerbations of chronic obstructive lung disease and the risk of hospital readmission.

Lay title: Can the levels of exhaled nitric oxide during an acute exacerbation of COPD predict which patients will be at higher risk of further hospital admissions over the next twelve months?

STUDY INVESTIGATOR(S)

Principal Investigator (A): Dr Francesco Piccolo[1]
Ph. 08 9462 5300
Fax 08 9462 5270
Email: francesco.piccolo@sjog.org.au
Principal Investigator (B): Dr David Manners[1]
Co-Investigator (A): Mr Simon Jones[1]

[1.] St John of God Midland Private and Public Hospital. Suite 1, Level 1, 1 Clayton Street, Midland 6056. Perth, Western Australia.

1. INTRODUCTION

Nitric oxide (NO) is a recognised biological mediator in humans and has been implicated in the pathophysiology of lung diseases including asthma and eosinophilic airway inflammation. NO is produced in the human lung and is present in exhaled breath. The measurement of fractional exhaled nitrous oxide (FeNO) has now been standardized for clinical use. Numerous studies have already provided evidence regarding the clinical applications of FeNO measurements. The role of FeNO measurements in *asthma* has been well established and practice guidelines regarding its clinical applications have been published (Dweik *et al.*, 2011). However, the exact role of FeNO measurements and its clinical implications remain unclear in the context of Chronic Obstructive Pulmonary Disease (COPD). This exploratory study aims to further clarify the utility of FeNO in the setting of acute exacerbations of COPD (AECOPD).

2. BACKGROUND

Fraction of Expired Nitric Oxide measurement

NO gas is produced in the epithelial cells of the bronchial wall in response to interleukin-4 and -13, which are produced locally by the TH2 cells, mast cells, and eosinophils. FeNO indicates the presence of pro-inflammatory cytokines due to eosinophilic airway inflammation. Advances in technology and standardization have made FeNO measurement simple and rapid permitting its use as a point-of-care biomarker in the assessment of inflammatory airways diseases.

Expired Nitric Oxide in Asthma

FeNO has been used as a marker for TH2-mediated airway inflammation in asthma and has been shown to correlate with airway inflammation and to be reduced by corticosteroid therapy. FeNO measurement are currently recommended in asthma to support the diagnosis of eosinophilic airway inflammation; determine the likelihood of steroid responsiveness; monitor airway inflammation and guide changes in anti-inflammatory therapy (Dweik *et al.*, 2011). In adults with asthma, a FeNO above 50 parts per billion (ppb) identifies patients who are likely to respond to steroids, while a FeNO below 25ppb identifies those who are not (Smith *et al.*, 2005).

Eosinophils and Expired Nitric Oxide in COPD

In patients with COPD increased, yet variable, eosinophil numbers have been detected in sputum, BAL samples and airway biopsies. However, compared with asthma, less is known about the role of eosinophils in the pathogenesis of COPD. This is despite the finding that sizable proportion of patients with COPD have eosinophilic inflammation (Saha e Brightling, 2006). Interest in the phenotyping of airway diseases has led to the recognition of an asthma-COPD overlap population in which some patients diagnosed with asthma also have features of COPD and vice versa. Patients with asthma-COPD overlap syndrome (ACOS) account for 15%–20% of COPD patients with greater disease morbidity compared with those with COPD alone. Although the underlying pathobiology of ACOS is largely unclear, recent genomic studies have demonstrated a potential role of TH2 inflammation and eosinophil activation.

A recent review (Bafadhel *et al.*, 2017) on the clinical significance of peripheral eosinophil counts and COPD management suggest that circulating eosinophils during stable COPD may help predict risk of mortality and risk of exacerbations. Additionally, in patients at the onset of an acute exacerbation blood eosinophilia may be used to identify those with worse outcomes and predict risk of further exacerbations (Vedel-Krogh *et al.*, 2016), hospital readmission (Couillard *et al.*, 2017), length of hospital stay, response to corticosteroids (Pizzichini *et al.*, 1998; Brightling *et al.*, 2000) and mortality (Hospers *et al.*, 2000). Despite the above findings, results from trials evaluating the use of eosinophils in guiding the treatment of COPD, both during stable disease and exacerbations, are still pending.

FeNO indicates the presence of pro-inflammatory cytokines due to eosinophilic airway inflammation and its measurement offers an attractive potential biomarker that may be useful for risk stratification and management of COPD patients. However, little is known about the FeNO levels in patients with COPD and ACOS and the exact role of FeNO measurements in these patients is still being defined.

To date, studies assessing FeNO in COPD patients have identified the following:

1. FeNO measurements in COPD patients
    - The median FeNO concentration in stable COPD patients is 15-20ppb (Beg *et al.*, 2009; Rouhos *et al.*, 2011; Donohue *et al.*, 2014) and higher during acute exacerbation of COPD 17-25 ppb , *(Zhu et al. Int J Clin Exp Med 2016; 9: 10565-10571)*. On average, these levels are lower than those seen with asthma.
    - Repeatability of FeNO in moderate to very severe stable COPD subjects (n= 20) has been shown to be adequate (Rouhos *et al.*, 2011).

2. FeNO in stable COPD patients
    - FeNO is significantly elevated compared with normal controls. The elevations however appear to be less than in asthmatic subjects (Beg *et al.*, 2009).
    - FeNO predicts a clinically significant increase in FEV1 in response to short term treatment with corticosteroids. In these patients , a high FeNO > 50ppb only had a modest positive predictive value (67%) for steroid responsiveness, however a low FeNO <25ppb had a high negative predictive value (87%) (Kunisaki *et al.*, 2008; Dummer *et al.*, 2009).
    - Greater FeNO variability has been reported in patients with stable COPD who subsequently develop exacerbations *(de Laurentis et al Pulm Pharmacol Ther 2008; 21:689-693).*

    The clinical implication of these findings is that FeNO levels in stable COPD patients may aid deciding in whom to initiate or escalate inhaled corticosteroid therapy.

3. FeNO during acute exacerbations COPD
    - FeNO has been shown to be elevated in COPD exacerbations (Bhowmik *et al.*, 2005). However this elevation is significantly lower than in patients with acute exacerbations of bronchial asthma *(Zhu et al Int. J. Clin. Exp Med. 2016).*
    - In patients admitted with COPD exacerbations FeNO on admission was a strong predictor of a clinically significant increase in FEV1 following treatment. FeNO below the optimum cut-point of 27ppb predicted the absence of any significant improvement in spirometry with a negative predictive value of 85% (Antus *et al.*, 2010).

    The clinical implication of these findings is that FeNO levels may predict the response to treatment during acute exacerbations of COPD.

4. Risk of recurrent exacerbations
    - Antus et al.'s *(Acta Physiologica Hungarica 2013; 100: 469-77)* follow-up retrospective study of COPD patientsadmitted with an acute exacerbation found a correlation between *low* FeNO levels (<27ppb) and increased number of exacerbations per patient year and hospitalization days due to further exacerbations over a 3 year period.

    This finding should be interpreted with caution as it is opposite to what was seen with peripheral eosinophil counts being correlated to risk of readmission. (Couillard *et al.*, 2017)

5. FeNO mechanism in COPD
    - Exhaled nitric oxide correlates with eosinophilic airway inflammation in COPD. FeNO was higher in stable COPD patients with sputum eosinophilia (29ppb) than those without (18ppb) (Chou *et al.*, 2014).
    - However, it remains unclear what an elevated FeNO in AECOPD is due to and if it is acting as a surrogate marker of eosinophilic airway inflammation or if an alternative aspect of airway pathophysiology is at play.

Clinical implications of this study

COPD is one of the leading causes of disability and mortality worldwide. Patients with COPD may suffer recurrent exacerbations. COPD exacerbations are complex events usually associated with increased airway inflammation, increased mucous production and marked gas trapping. These changes contribute to increased dyspnea that is the key symptom of an exacerbation. Other symptoms include increased sputum purulence and volume, together with increased cough and wheeze. COPD exacerbation result in a worsening of symptoms and reduction in lung function that may not be recovered in a proportion of patients. Furthermore, exacerbations are associated with an impaired quality of life, reduced survival, and a high healthcare expenditure. The latter mainly results from admission to hospital which is frequently a consequence of an exacerbation. Prevention of exacerbations is therefore an important goal in the management of stable COPD, although knowledge about which factors relate to COPD exacerbations or hospitals admissions for exacerbations is currently very limited.

Patients who suffer a COPD exacerbation are at risk of further hospital admissions, with up to 15% and 35% requiring readmission at 30 and 90 days respectively. Risk for hospital readmission in COPD are increased age, increased severity of airflow obstruction (GOLD stage 4), reduced physical activity and associated comorbidities. One of the predictors of hospital readmission for AECOPD is a previous admission in the preceding 12 months with risk of readmission increasing with every additional admission event. Identifying potentially reversible causes of readmission and targeting specific interventions to a subgroup of these at risk patients may aid in modifying their long-term and short-term outcomes.

FeNO measurement is a simple and rapid point-of-care test that can be performed easily in the in-patient as well as the out-patient setting. This exploratory study aims to further clarify the role of FeNO in the setting of AECOPD and assess its association with risk of readmission. Identifying patients at greater risk of readmission may potentially help target interventions in this population.

3. AIM(S) OF STUDY

Exploratory study to evaluate FeNO levels in patients during and following recovery from an admission with an acute exacerbation of COPD.

4. OBJECTIVES

The objectives of the study are:

1. To determine if FeNO levels measured in the first 24 hours of admission to hospital for an AECOPD correlates to readmission risk at 12 months (and time to readmission).
2. To determine if FeNO levels measured in the first 6 weeks after discharge from hospital for an AECOPD correlates to readmission risk at 12 months (and time to readmission).

3. To determine if FeNO levels measured in the first 24 hours of admission to hospital for an AECOPD predict FEV1 improvement at 6 week follow-up.
4. To determine if FeNO levels measured in the first 24 hours of admission to hospital for an AECOPD predict CAT improvement at 6 week follow-up.

5. To describe the relationship between FeNO levels measured in the first 24 hours of admission to hospital for an AECOPD and blood eosinophil count.
6. To describe changes in FeNO levels between the first 24 hours of admission to hospital for AECOPD and at 6 week follow-up.

5. HYPOTHESIS

5b. Primary Hypothesis

There is evidence that the presence of a raised blood eosinophil count in patients with an AECOPD may predict the risk of hospital readmission(Couillard *et al.*, 2017). FeNO correlates with eosinophilic airway inflammation in COPD (assessed by measuring sputum eosinophilia). (Chou *et al.*, 2014)

We hypothesize that patients with higher FeNO levels during and/or at 6 weeks recovery from an admission with an AECOPD are at higher risk of hospital readmission in the subsequent 12 months.

5b. Secondary Hypotheses

FeNO correlates with eosinophilic airway inflammation in COPD, a *potentially* reversible and steroid responsive component of airflow obstruction in patients with an acute exacerbation.

We hypothesize that patients with higher FeNO levels during and/or at 6 weeks recovery from an admission with an AEOPD are more likely to respond to steroid (inhaled and/or systemic) therapy with improved FEV1 measurements.

6. STUDY DESIGN

Single centre prospective observational cohort study.

7. STUDY SETTING/LOCATION

Single centre study conducted at St John of God Midland Public and Private Hospitals (SJGMPPH).

8. STUDY POPULATION

The study population is consecutive patients admitted to St John of God Midland Private and Public hospital with a primary diagnosis of severe acute exacerbation of COPD (AECOPD). An AECOPD is defined as acute worsening of respiratory symptoms that results in additional therapy: antibiotics and/or systemic corticosteroids. Admission to hospital usually implies severe exacerbation of COPD. As this is an exploratory study a total of **80** patients will be recruited.

9. ELIGIBILITY CRITERIA

9a. Inclusion criteria

- Age ≥ 40 years
- Smoking history ≥ 15 pack years
- Suspected or Known COPD defined as a FEV1/FVC ratio of <70% on spirometry
- Hospital admission with primary diagnosis of AECOPD

9b. Exclusion criteria

- Patients who do not have airflow obstruction on spirometry (FEV1/FVC<70%)
- Patients in acute respiratory failure requiring non-invasive positive pressure ventilation or invasive mechanical ventilation
- Patients requiring ionotropic support
- Patients with concurrent diagnosis of bronchiectasis, interstitial lung disease, pulmonary embolism or acute cardiac failure
- Overseas and Interstate visitors

10. STUDY OUTCOMES

10a. Primary Outcome

- Hospital re-admission for COPD within 12 months defined as admitted to hospital, excluding emergency department presentation only, with discharge diagnosis on the discharge summary being “Exacerbation of COPD”.

10b. Secondary Outcome(s)

- Time to hospital re-admission for COPD (up to 12 months)
- Repeat exacerbation of COPD within 12 months, defined as an acute worsening of respiratory symptoms that results in increased dose of systemic corticosteroids and /or antibiotics. This outcome will be self reported.
- Change in FeNO levels between Day 1 of admission and on follow-up visit at 6 weeks.
- Change in FEV1, FVC, FEV1/FVC between Day 1 of admission and on follow-up visit at 6 weeks.
- Change in CAT score between Day 1 of admission and on follow-up visit at 6 weeks.

11. STUDY PROCEDURES

11a. Recruitment of participants

Screening will take place before consent. The respiratory physician involved in the study will approach potential study participants within 24 hours of admission for a primary diagnosis of AECOPD. If they fulfill inclusion criteria and have no exclusion criteria they will be invited to participate in this study. They will be provided with written information about the research and given the opportunity to ask questions regarding participation. The participant will have up to 2 hours to decide if they wish to participate. Once informed consent is given they will be considered participants. We aim to recruit 80 participants. From a small audit (10 patients) performed in 2017 we expect that 60% of patients asked to participate will be able perform FeNO and spirometry testing essential for recruitment. Those who cannot complete either FeNO or spirometry will be excluded from final analysis as they cannot contribute to the primary outcome. However, as this is a potential source of bias we will collect all other data and follow-up outcomes from these patients also. We expect 12 months will be necessary to recruit 80 patients who can perform both FeNO and Spirometry on admission.

11b. Randomisation

This is a prospective observational cohort study. No randomization is required. No case matching is required.

11c. Study procedure

We will approach potential study participants within 24 hours of admission for a primary diagnosis of AECOPD. If they fulfill inclusion criteria and have no exclusion criteria they will be asked to participate in this study. Once informed consent is given they will be considered participants. Patient questionnaire, FeNO and spirometry testing will be performed at Day 1 (recruitment day) and at 6-week follow-up appointment. A further questionnaire via phone contact will be performed at 3, 6, 9 & 12 months. If the participant cannot be contacted by phone, the study will contact the nominated next-of-kin and general practitioner. The patient's general practitioner will be informed of study participation. This study does not involve any treatment intervention. All additional tests, except FeNO measurement, are considered part of usual care. Additional tests include spirometry and blood testing (FBC, IgE and RAST) and will be used to identify individuals who may have Asthma COPD Overlap Syndrome (ACOS). These tests can be "added on" to bloods taken on admission. The study does not

require additional follow-up appointments as the 6 week follow-up of these patients is part of usual care. An extra phone contact with the patients will be made at 3, 6, 9 & 12 months.

Day one:

- Location: SJOG hospital medical ward inpatient room
- Duration: 30 minutes
    - Informed Consent – 10 minutes
    - Questionnaire – 5 minutes
    - FeNO testing – 5 minutes
    - Spirometry testing - 10 minutes
- Baseline data collection form
    - Questionnaire –
        - patient demographics, Charlson Comorbidity Index, COPD Assessment test, modified MRC dyspnea scale, Hospital Anxiety and Depression Scale
    - Laboratory blood tests –
        - Full blood picture as per usual medical care. Retrieved from hospital pathology program.
        - IgE and RAST testing added – This is usual clinical care to identify individuals who may have ACOS.
    - Radiology – CXR as per usual medical care. Retrieved from hospital radiology program
    - Treatment – as per usual medical care documented from hospital patient medical file
- FeNO bedside measurement
- Spirometry testing

Early Post-Hospital Discharge:

- Researcher staff only – interrogating electronic medical records to determine discharge date and corticosteroid medication prescriptions during and after hospitalization.

6 week follow-up:

- Location: SJOG hospital medical outpatient clinic
- Duration: 30 minutes
    - Questionnaire – 5 minutes. (COPD Assessment test, modified MRC dyspnea scale)
    - FeNO testing – 5 minutes
    - Spirometry testing - 10 minutes
    - Blood testing – 10 minutes
- 6 week data collection form
- Laboratory blood tests – FBC, CRP, IgE
- FeNO bedside measurement
- Spirometry testing

3,6,9 & 12 month follow-up:

- Location: Phone contact only
- Duration: 5 minutes
    - Questionnaire – 5 minutes
- 3, 6, 9 &12 month data collection form

- If the patient is unable to be contacted, consent will have been obtained to contact the nominated next of kin and General Practitioner to obtain any hospital admission discharge summary to determine the primary outcome.

11d. Measurement tools used

- Fraction of Expired Nitric Oxide
    - FeNO measurement will be performed using the *NIOX VERO*® device. It is able to measure expired nitrous oxide within a range of 5 to 300 ppb (accuracy +/- 5 ppb of measured values ≤ 50 ppb). NIOX devices are the most widely used devices for measuring airway inflammation in clinical practice and clinical studies. It requires the patient to exhale at a constant rate for at least 10 seconds, which some patients may find difficult to perform. It provides a measurement of expired NO within 60 seconds of test. It is portable and battery powered and thus suitable for ward and clinic environments.
- Spirometry
    - Spirometry will be performed as per ATS guidelines (Miller *et al.*, 2005) with the *EasyOne Spirometer*® device. Measures recorded include FEV1, FVC and FEV1/FVC ratio. Both measured values and percent of predicted values will be recorded. Presence and severity of airflow obstruction will be classified as per GOLD spirometry criteria.
    - The *EasyOne Spirometer*®, has been chosen because it provides a high degree of accuracy, robustness, portability, and ease of storage. It can be used easily on the ward and in the clinic environment, it operates on batteries and requires no calibration. It has been previously used in other studies.
- COPD Assessment Test (CAT)
    - The CAT is a patient-completed instrument that can quantify the impact of COPD on the patient's health. Validation studies have shown that it has properties very similar to much more complex health status questionnaires such as the St George's Respiratory Questionnaire. Systematic reviews confirm that the CAT provides reliable measurement of health status and is responsive to change with treatment and exacerbations. Since 2013 it has been incorporated as the preferred measure of symptomatic impact of COPD into clinical assessment schemes and is also included in the COPD Foundation guide.
    - The test is comprised of eight questions pertaining to cough, sputum, chest tightness, exercise tolerance, ability to perform activities of daily living, confidence in leaving the home, sleep and energy levels. Each question is scored on a 6-point scale (0 to 5) yielding a total possible score of 40 for the questionnaire. The total CAT score provides a broad clinical picture of the impact of COPD on an individual patient with scores of >30, 21-30, 10-20 and <10 corresponding to very high, high, moderate and low impact respectively. A total score of 5 is the upper limit of normal in a healthy non-smoker(Jones *et al.*, 2011). A systematic review (Gupta *et al.*, 2014) that included 36 studies carried out in 32 countries reported the CAT to be reliable, valid and responsive as more complex HRQoL instruments.
    - Although the minimum clinically important difference in the total CAT score is unclear, CAT scores in patients with moderate-severe exacerbations are

approximately 5 units higher than in those who have stable COPD. Patients responding to treatment for their exacerbation have been shown to reduce their CAT score by 2 units in 14 days.

- Modified MRC (mMRC) dyspnea scale
    - mMRC dyspnoea scale quantifies the effect of breathlessness on daily activities(Celli *et al.*, 2004). The test comprises five statements that describe almost the entire range of respiratory disability from none (Grade 1) to almost complete incapacity (Grade 5). It can be self-administered by asking subjects to choose a phrase that best describes their condition. All the questions relate to everyday activities and are generally easily understood by patients. A score can usually be obtained in a few seconds. The MRC breathlessness scale does not quantify breathlessness itself. Rather, it quantifies the disability associated with breathlessness by identifying that breathlessness occurs when it should not (Grades 1 and 2) or by quantifying the associated exercise limitation (Grades 3–5).
    - There is up to 98% agreement between observers recording MRC breathlessness scores. The score correlates well with the results of other breathlessness scales, lung function measurements and with direct measures of disability such as walking distance. Its main disadvantage over other more complex scales is its relative insensitivity to change. Changes can be demonstrated, for example, after lung surgery but it is uncommon for individuals to improve or deteriorate by an entire grade over relatively short periods.
    - The MRC breathlessness scale is widely used to describe patient cohorts and stratify them for interventions such as pulmonary rehabilitation in COPD. It can predict survival and it is advocated as complementary to FEV1 in describing disability in those with COPD .
- Charlson Comorbidity Index (CCI)
    - The CCI predicts the one-year mortality for patients with a range of co-morbid conditions. Each of 22 comorbidities is assigned a score of 1, 2, 3 or 6 depending on the risk of death. The sum of the score predicts mortality and is adjusted for age. It has been extensively validated and used in numerous trials.
    - https://www.mdcalc.com/charlson-comorbidity-index-cci
- Hospital Anxiety and Depression Scale (HADS)
    - Anxiety has previously been linked to hospital readmission for COPD. The HADS is a 14 question, self-administered survey focusing on both anxiety and depressive symptoms. It is scored ordinally. It has been extensively validated and is recommended by the National Institute for Health and Care Excellence as a tool to diagnose depression and anxiety.
- Questionnaire
    - Demographic, smoking history, hospital admission history
- Medication Chart
    - Usual medication and acute pharmacotherapy information
- Observation chart
    - Assessment of admission physical observation including temperature, respiratory rate, pulse rate, blood pressure
- Biological specimens
    - Full blood count – to assess eosinophil blood count. At day 1 and 6 week follow-up.

- IgE level. At day 1 and 6 week follow-up.
- RAST dust mite, pollen and grass mix, animal epithelia mix, mould. At day 1 only.

11e. Safety considerations/Patient safety

This observational study does not involve any treatment interventions. Treatment decisions will be managed by the treating physician, in cooperation with the patient, independently of the study and its researchers. At SJOG Midland, treating physicians are specialist general physicians who are independent of the study personnel, minimizing conflict or duality of interest between treating doctors and the study team. All tests performed, except the measurement of FeNO, are considered part of usual care. The additional FeNO measurement using the *NIOX VERO*® device can be difficult for some patients to perform, especially when they are acutely unwell. Therefore, despite the test being very safe it may cause some minor distress to some patients.
Administering the research questionnaire may have adverse psychological effects on susceptible individuals. Particularly questions pertaining to their level physical functioning and regarding the presence of anxiety or depression symptoms.
Any adverse events of the test or questionnaire will be recorded and reported to the treating physician with the participant's consent.

11f. Data monitoring
Patient questionnaires and CRFs will be stored in a locked filing cabinet in a secure medical office of Midland Physician Service at St John of God Hospital Midland. Only staff involved in the study will review these forms.
Data will be entered in a computer spreadsheet in a de-identified form. This password protected spreadsheet will be saved in a password protected personal computer. Only staff involved in the study analysis will review these forms.

12. STATISTICAL CONSIDERATIONS AND DATA ANALYSIS

12a. Sample size and statistical power

This is an observational study without a pre-specified sample size. Based on pilot data and numbers of COPD admissions, we anticipate 80 participants will be both feasible and sufficient to examine the primary outcome.

12b. Statistical methods

Predictors for the primary outcome (readmission for COPD exacerbation) will be identified by using a multivariate logistic regression model incorporating FeNO level and other known and suspected factors associated with COPD readmissions. Associations between FeNO and readmission will be presented as odds ratios. Systemic steroids can affect FeNO measurements. Therefore, outcomes will also be analysed by dose of systemic corticosteroid prior to FeNO measurement.

Predictors of the secondary outcomes (time to readmission for repeat exacerbation of COPD and time to repeat exacerbation) will be identified by using a Cox Proportional Hazards regression model or logistic regression model as appropriate incorporating FeNO level and other known and suspected

factors associated with COPD readmissions. Associations between FeNO and readmission will be presented as hazard ratios (Cox Proportional Hazards model) or odds ratios (logistic regression model).

13. ETHICAL CONSIDERATIONS

The study will be conducted in full conformance with principles of the "Declaration of Helsinki", Good Clinical Practice (GCP) and within the laws and regulations of Western Australia. Ethics approval will be sought from SJOG.

Patients will be provided with information sheets regarding study participation. Informed consent will be required for participation. The patients will be aware that declining participation will not result in any change to the quality of their care. Ongoing verbal consent will be sought at each follow-up appointment and phone contacts.

The patient will only undergo one additional test, FeNO, that is not considered to be part of usual care for people having an exacerbation of COPD. The FeNO test is negligibly invasive as it only involves exhaling through a user-operated, handheld device. Harms associated with the FeNO test are limited to possible distress or discomfort associated with the exhalation maneuver in patients who are suffering an acute respiratory exacerbation.

Consent for the study will specifically include consent for the study to contact the nominated next-of-kin and general practitioner for the purposes of 1) follow-up 3, 6, 9 & 12 month phone calls if the participant cannot be contacted and 2) to gain access from the general practitioner for hospital admission discharge summaries, other than SJGMPPH admissions, during the study period.

14. OUTCOMES AND SIGNIFICANCE

To date, studies assessing FeNO in COPD are limited and little is known about the FeNO levels in patients with AECOPD. This exploratory study aims to further clarify the utility of FeNO in the setting of hospitalised AECOPD and the subsequent risk of hospital readmission in these patients. Potential future research stemming from this work may be to target specific interventions in patients identified to be at higher risk of readmission.

15. REFERENCES

World Medical Association Declaration of Helsinki (1964)
Note for guidance on good clinical practice (CPMP/ICH/135/95 - Annotated with TGA comments)
National Statement on Ethical Conduct in Human Research (2007)

ANTUS, B. et al. Relationship between exhaled nitric oxide and treatment response in COPD patients with exacerbations. **Respirology,** v. 15, n. 3, p. 472-7, Apr 2010. ISSN 1440-1843. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/20210889 >.

BAFADHEL, M.; PAVORD, I. D.; RUSSELL, R. E. K. Eosinophils in COPD: just another biomarker? **Lancet Respir Med,** v. 5, n. 9, p. 747-759, Sep 2017. ISSN 2213-2619. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/28601554 >.

BEG, M. F. et al. Exhaled nitric oxide in stable chronic obstructive pulmonary disease. **Ann Thorac Med,** v. 4, n. 2, p. 65-70, Apr 2009. ISSN 1817-1737. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/19561927 >.

BHOWMIK, A. et al. Effects of exacerbations and seasonality on exhaled nitric oxide in COPD. **Eur Respir J,** v. 26, n. 6, p. 1009-15, Dec 2005. ISSN 0903-1936. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/16319329 >.

BRIGHTLING, C. E. et al. Sputum eosinophilia and short-term response to prednisolone in chronic obstructive pulmonary disease: a randomised controlled trial. **Lancet,** v. 356, n. 9240, p. 1480-5, Oct 2000. ISSN 0140-6736. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/11081531 >.

CELLI, B. R. et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. **N Engl J Med,** v. 350, n. 10, p. 1005-12, Mar 2004. ISSN 1533-4406. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/14999112 >.

CHOU, K. T. et al. Exhaled nitric oxide predicts eosinophilic airway inflammation in COPD. **Lung,** v. 192, n. 4, p. 499-504, Aug 2014. ISSN 1432-1750. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/24816967 >.

COUILLARD, S. et al. Eosinophils in COPD Exacerbations Are Associated With Increased Readmissions. **Chest,** v. 151, n. 2, p. 366-373, Feb 2017. ISSN 1931-3543. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/27746201 >.

DONOHUE, J. F. et al. Characterization of airway inflammation in patients with COPD using fractional exhaled nitric oxide levels: a pilot study. **Int J Chron Obstruct Pulmon Dis,** v. 9, p. 745-51, 2014. ISSN 1178-2005. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/25053884 >.

DUMMER, J. F. et al. Predicting corticosteroid response in chronic obstructive pulmonary disease using exhaled nitric oxide. **Am J Respir Crit Care Med,** v. 180, n. 9, p. 846-52, Nov 2009. ISSN 1535-4970. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/19661244 >.

DWEIK, R. A. et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. **Am J Respir Crit Care Med,** v. 184, n. 5, p. 602-15, Sep 2011. ISSN 1535-4970. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/21885636 >.

GUPTA, N. et al. The COPD assessment test: a systematic review. **Eur Respir J,** v. 44, n. 4, p. 873-84, Oct 2014. ISSN 1399-3003. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/24993906 >.

HOSPERS, J. J. et al. Eosinophilia is associated with increased all-cause mortality after a follow-up of 30 years in a general population sample. **Epidemiology,** v. 11, n. 3, p. 261-8, May 2000. ISSN 1044-3983. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/10784241 >.

JONES, P. W.; TABBERER, M.; CHEN, W. H. Creating scenarios of the impact of COPD and their relationship to COPD Assessment Test (CAT™) scores. **BMC Pulm Med,** v. 11, p. 42, Aug 2011. ISSN 1471-2466. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/21835018 >.

KUNISAKI, K. M. et al. Exhaled nitric oxide, systemic inflammation, and the spirometric response to inhaled fluticasone propionate in severe chronic obstructive pulmonary disease: a prospective study. **Ther Adv Respir Dis,** v. 2, n. 2, p. 55-64, Apr 2008. ISSN 1753-4658. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/19124359 >.

MILLER, M. R. et al. Standardisation of spirometry. **Eur Respir J,** v. 26, n. 2, p. 319-38, Aug 2005. ISSN 0903-1936. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/16055882 >.

PIZZICHINI, E. et al. Sputum eosinophilia predicts benefit from prednisone in smokers with chronic obstructive bronchitis. **Am J Respir Crit Care Med,** v. 158, n. 5 Pt 1, p. 1511-7, Nov 1998. ISSN 1073-449X. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/9817701 >.

ROUHOS, A. et al. Repeatability of exhaled nitric oxide measurements in patients with COPD. **Clin Physiol Funct Imaging,** v. 31, n. 1, p. 26-31, Jan 2011. ISSN 1475-097X. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/21143751 >.

SAHA, S.; BRIGHTLING, C. E. Eosinophilic airway inflammation in COPD. **Int J Chron Obstruct Pulmon Dis,** v. 1, n. 1, p. 39-47, 2006. ISSN 1176-9106. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/18046901 >.

SMITH, A. D. et al. Exhaled nitric oxide: a predictor of steroid response. **Am J Respir Crit Care Med,** v. 172, n. 4, p. 453-9, Aug 2005. ISSN 1073-449X. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/15901605 >.

VEDEL-KROGH, S. et al. Blood Eosinophils and Exacerbations in Chronic Obstructive Pulmonary Disease. The Copenhagen General Population Study. **Am J Respir Crit Care Med,** v. 193, n. 9, p. 965-74, May 2016. ISSN 1535-4970. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/26641631 >.