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PACE Study

PACE
Point of care testing to target antibiotics for chronic obstructive pulmonary disease exacerbations

Primary care use of a C-Reactive Protein (CRP) Point of Care Test (POCT) to help target antibiotic prescribing to patients with Acute Exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD) who are most likely to benefit

Summary:

PACE is a randomised controlled trial that aims to evaluate whether using a CRP point of care test (POCT) results in better targeting of antibiotic treatment in patients with AECOPD than usual care informed by NICE and GOLD guidelines.

Background:

- Over 70% of patients presenting with AECOPD in primary care are prescribed an antibiotic
- Nearly a third of exacerbations are triggered by environmental factors and not infections, and that in those that are likely triggered by an infection, pathogenic respiratory viruses can be detected in approximately 50% while pathogenic bacteria are isolated in only 20-58%
- Current antibiotic prescribing recommendations for GPs are generally based on symptoms alone
- There is growing interest in the potential for biomarkers (such as C-Reactive Protein (CRP)) to help predict benefit from antibiotic treatment for AECOPD.
- Overuse of antibiotics drives increased antimicrobial resistance.

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Primary Objective:

To determine whether the addition of a CRP POCT to current best practice based on NICE guidelines for managing an AECOPD leads to a reduction in antibiotic consumption without negatively impacting on COPD health status, compared with current best practice alone.

To meet this objective, we will assess:

- Antibiotic consumption (any consumption of antibiotics vs. no consumption of antibiotics) over the **first four weeks following randomisation**.

- Recovery in terms of COPD health status, which will be assessed at two weeks post-randomisation using the **CCQ**.

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Secondary Objectives:

To assess the effect of using a CRP POCT for AECOPD in primary care on:

- Prevalence of resistant bacteria in sputum (or throat swab) at 4 weeks
- COPD health status over time (weeks 1, 2 and 4)
- Health utility, measured using the EQ-5D at 1, 2 and 4 weeks
- Antibiotic prescribing at the index consultation
- Use of other COPD treatments including oral steroids during the first four weeks;
- Adverse effects from antibiotics and other medication prescribed for their AECOPD during the first four weeks
- Primary and secondary care consultations (including out of hours, A&E visits and hospitalisations) during the subsequent 6 months
- Costs and cost-effectiveness from a health service perspective
- Incidence of pneumonia during the first 4 weeks and from the 4-week follow up to 6 months.
- Disease-specific HRQoL (CRQ-SAS) at 6 months

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Participant Flow chart

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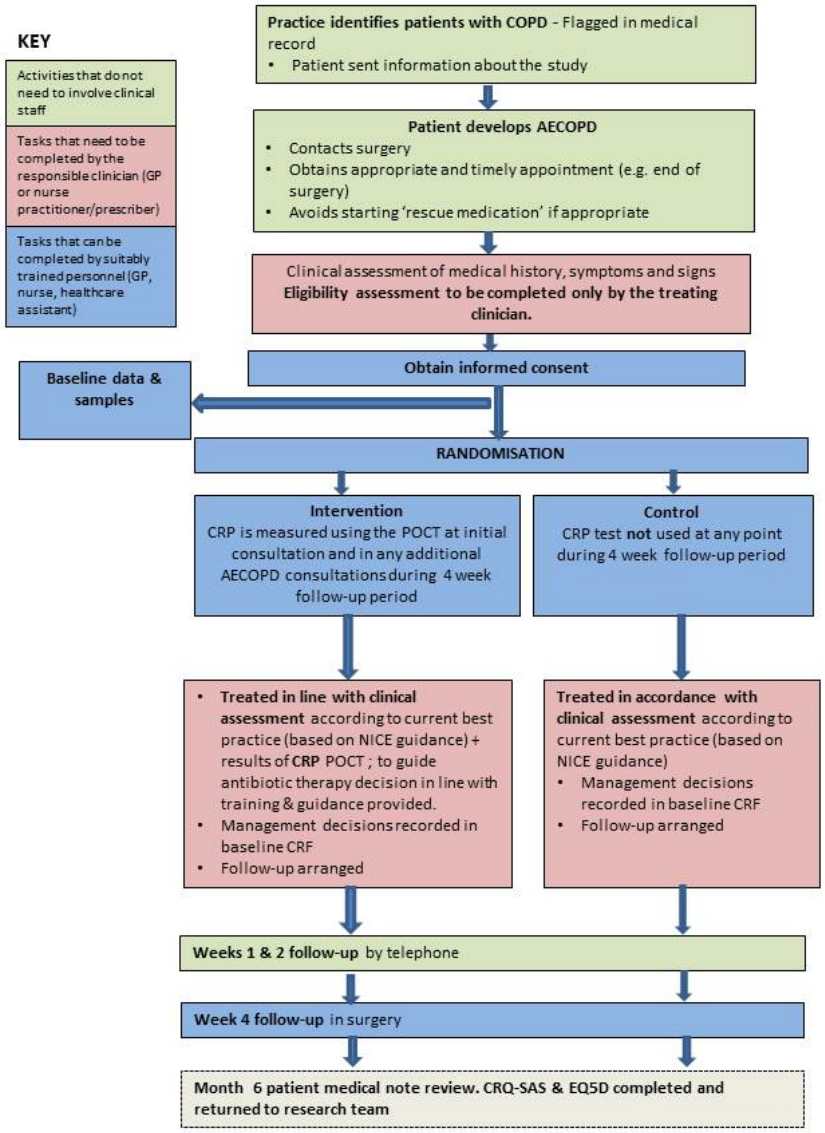

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Patient Searches and Mail out

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1) A list of patients who may be eligible for the study (should they develop exacerbations) must be created. Please use your GP system (e.g. EMIS, VISION, etc.) COPD QOF register to identify all eligible patients for the study.

2) Alternatively you could create a new search on the current practice population, for patients 40 years of age or more and using the read-codes (shown in the study manual and the PACE website).

3) Please go through the list of patients and identify and exclude (please see Participant Inclusion/exclusion criteria in PACE Study Site File) patients who may not be able to take part in the study for e.g. House bound patients, patients who may not be able to provide consent, life limiting malignancy, severe mental illnesses etc.

4) Mail merge the PACE invite letter using your practice header addressed to all the patients on the final list. Please also include the PACE patient information sheet (PIS), summary PIS and patient card with this letter to complete the study pack.

5) Finally mail out these study documents to the respective patients as soon as possible

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Patient Searches and Mail out – cont:

- **Put a flag** in all approached patients' notes that they are potentially eligible for the PACE Study. Should an identified patient contact the surgery with a suspected exacerbation, they should be booked into a special PACE appointment, so please make sure that reception staff are aware of this.

- Should an **eligible** patient who has **not** received the Invitation Letter present at a routine surgery session with an exacerbation of COPD, please consider them for the PACE Study.

- It is recommended that you reserve a consultation slot at the end of surgery sessions for potentially eligible AECOPD patients

- Please approach eligible patients opportunistically in routine surgery sessions as well as patients that are booked into special PACE appointments. Patients should be recruited **only once** into PACE.

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Use of 'Rescue Packs'

- Patients that have started taking antibiotics prior to being assessed will not be eligible to participate

- The invite letter asks the patient not to take rescue medication before seeing their GP if they want to take part in the study

- In order to give as many patients the opportunity to take part as possible we would encourage you to suggest to your COPD patients who are not housebound that they contact the practice for an early assessment of suspected acute exacerbations rather than start using a 'rescue pack'.

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Patient Presents to surgery:

Patient contacts the surgery with an exacerbation of their COPD, which has been on-going for **no less than twenty-four hours and no more than 21 days**, and expresses an interest in taking part in the PACE study, they should be invited to an appointment that day to attend the surgery

Eligibility Assessment:

- carried out by responsible clinician (GP or nurse practitioner)

Informed consent:

- Carried out by suitably trained personnel – GP, nurse, healthcare assistant

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Eligibility Criteria

Inclusion Criteria

- Has a current acute exacerbation (presenting with at least one of the following: Increased dyspnoea, increased sputum volume, increased sputum purulence) that has lasted for at least 24 hours and no longer than 21 days
- Diagnosis of COPD in clinical record/on COPD Practice register
- Age 40 years or more
- Able to provide informed consent
- Patient should be able to provide the primary outcome data at 2 and 4 weeks within the expected windows

Exclusion Criteria

- The responsible clinician feels urgent referral to hospital is necessary
- Severe illness (e.g. suspected pneumonia, tachypnoea >30 breaths per minute, respiratory failure)
- Concurrent infection at another site (e.g. UTI, Cellulitis) that is likely to produce a systemic response
- Past history of respiratory failure or mechanical ventilation
- Currently on antibiotics or has had antibiotics for this acute exacerbation of COPD
- Active inflammatory condition (e.g. Flare up of rheumatoid arthritis, gout or polymyalgia rheumatica)
- Has cystic fibrosis, a current tracheostomy or bronchiectasis
- Immunocompromised (e.g. AIDS, taking systemic immunosuppressive therapy or receiving anti-cancer radiotherapy or chemotherapy)
- Currently pregnant
- Previously been recruited into the PACE study

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Baseline Visit:

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- Throat swabs and sputum samples taken. Assess sputum colour according to bronko chart
- Ensure patient completes the CCQ and EQ-5 D questionnaires (time to complete both is approx. 5 mins)
- Once all the above has been completed the patient can be **randomised**
- Following randomisation the remainder of baseline CRF03 must be completed – record CRP results, management

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Baseline Visit continued:

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- Ensure that the participant has received their participant pack
- Please take a moment to explain the participant booklet to the patient: they should record the medication that they have actually TAKEN in this (rather than medication they have been prescribed); this information will be collected from them in their Weeks 1 and 2 follow ups by a member of the research team (over the telephone)
- Please also ask them to complete the outcome measures CCQ and EQ5D on the day of both their Week 1 and Week 2 phone call (Day 8 & Day 15 respectively following baseline)
- Please also provide the patient with a pot (labelled with their PID) so that they can bring in a sputum sample at their Week 4 follow up visit
- Where possible, a 4 week follow up visit should be booked before the participant leaves the practice. If this is not possible at this baseline visit, please ensure you book the patient in for their 4 week appointment as soon as is possible.
- Let the patient know that a selection of participants will be contacted by telephone within two weeks of their four week follow-up assessment to invite them to take part in a qualitative interview by a member of the research team
- The Contacts Form, CRF02, should be completed and together with the consent Form should be FAXED to SEWTU as soon as possible.
-

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Swab and sputum sampling for PACE

Throat Swab

- ✓ Explain the procedure to the patient
- ✓ Take swab from the **posterior pharynx** without contaminating it in the mouth
- ✓ Put swab in transport container (labelled with study sticker) ensure securely placed.
- ✓ Complete request form.
- ✓ Send swab and form to laboratory.
- ✓ Document in notes.

Sputum sample

- ✓ Ask the participant to cough deeply and bring up the sputum from the lungs.
- ✓ Drinking plenty of fluids can help loosen the secretions
- ✓ Collect in study pot
- ✓ Label appropriately and transport promptly in the provided containers

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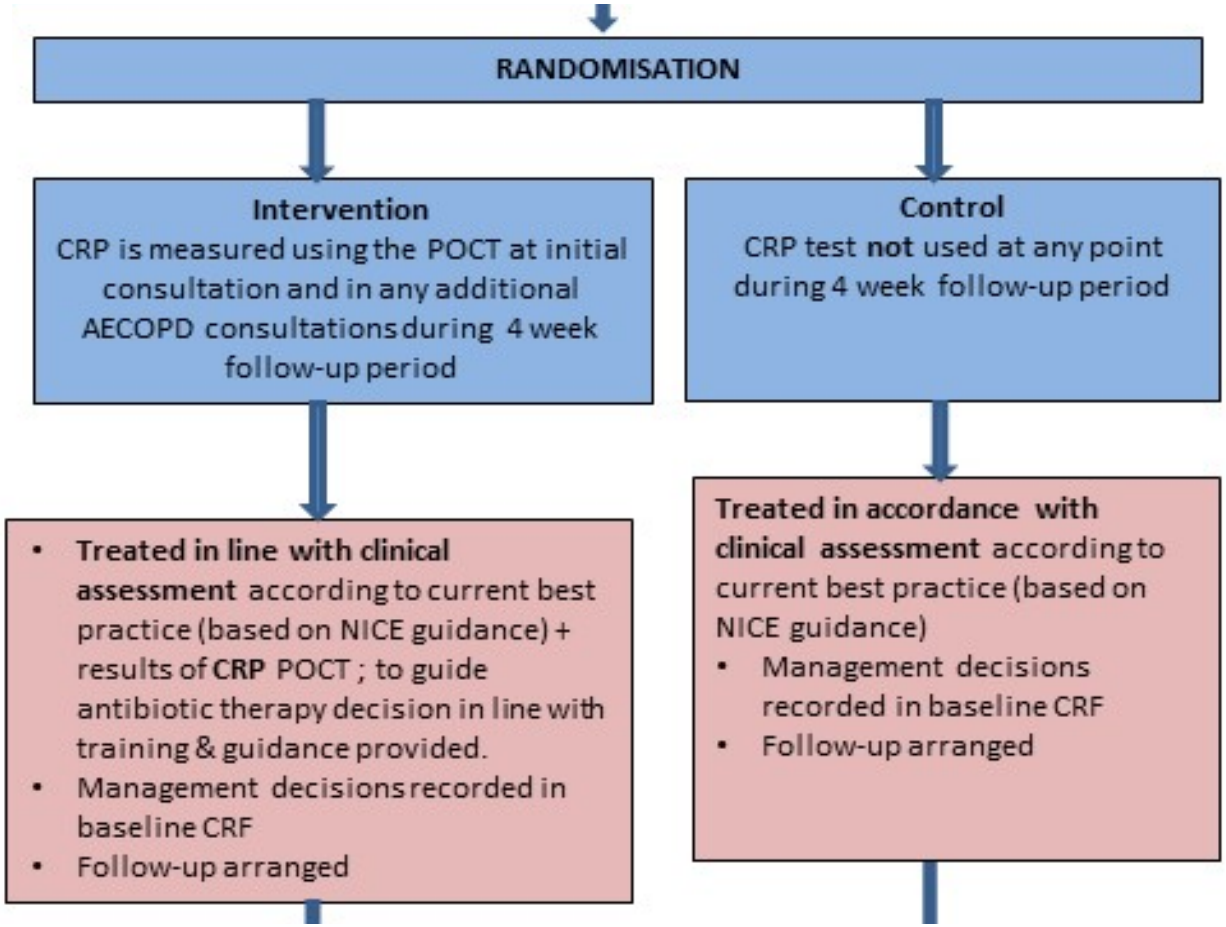

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Summary of NICE and GOLD guidance in relation to managing AECOPD - I

For further information, we recommend that you read the full NICE Guideline (which can be downloaded from the PACE website) and GOLD guidance document

Assessment (NICE)

Consider differential diagnosis:

Pneumonia
Pneumothorax
Left ventricular failure/pulmonary oedema
Pulmonary embolus
Lung cancer
Upper airway obstruction
Pleural effusion
Recurrent aspiration

Assessment of the severity of an exacerbation:

The following are signs of a severe exacerbation:
Marked dyspnoea
Tachypnea
Purse lip breathing
Use of accessory muscles (sternomastoid and abdominal) at rest
Acute confusion
New onset cyanosis
New onset peripheral oedema
Marked reduction in activities of daily living

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Summary of NICE and GOLD guidance in relation to managing AECOPD - II

Consider the need for hospital admission:
Most patients can be managed at home.

The following suggest the need for hospitalisation:
Not able to cope at home
Severe breathlessness
Poor general condition
Poor level of activity
Cyanosis
Worsened peripheral oedema
Impaired consciousness / acute confusion
On long term oxygen therapy
Rapid onset
Significant comorbidity
SaO2 < 90%

Investigations:
Sputum samples are not recommended in routine primary care practice.
Pulse oximetry is of value if there are clinical features of a severe exacerbation.

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Summary of NICE and GOLD guidance in relation to managing AECOPD - III

Treatment: Bronchodilators and Oral Corticosteroids

I) Bronchodilators

Use short-acting bronchodilators to treat breathlessness. These can be given either via a hand held inhaler with spacer or via nebuliser.

II) Consider use of oral corticosteroids

NICE recommends that in the absence of significant contraindications, oral corticosteroids should be considered in patients in the community who have an exacerbation with a significant increase in breathlessness which interferes with daily activities. (Grade B) NICE recommends prednisolone 30mg / day for 7 to 14 days. GOLD recommends 40mg / day for 5 days.

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Summary of NICE and GOLD guidance in relation to managing AECOPD - IV

Treating with Antibiotics

Assessing the need for antibiotics:

In patients randomised to the CRP arm, you will use the results of the CRP test to help guide your treatment decision.

In patients randomised to usual care, you will have to make a clinical decision based on your best assessment of the patient and guided by NICE and GOLD guidelines.

NICE recommends the use of antibiotics in patients with a history of more purulent sputum.

GOLD recommends use of antibiotics in patients with increased sputum purulence and either increased dyspnoea or increased sputum volume.

However, in all patients the decision to prescribe antibiotics should be based on a comprehensive assessment of the likely risks and benefits given:

- The patient's underlying health status (COPD severity, co-morbidities, frailty), Clinical features of the current exacerbation (including the severity of the exacerbation and the degree of sputum purulence).

- In patients randomised to CRP, the results of the CRP test will also contribute to this assessment.

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Interpretation of CRP results:

CRP Result	Interpretation
< 20	Antibiotics are unlikely to be beneficial and usually should not be prescribed.
20-40	Antibiotics may be beneficial – mainly if purulent sputum is present. You may decide to prescribe antibiotics after taking into account the patient's underlying health status and the features of the current exacerbation.
> 40	Antibiotics are likely to be beneficial. Consider prescribing antibiotics unless the patient is assessed as being at lower risk of complications and unlikely to have a bacterial infection (no increased sputum purulence and no features suggesting severe exacerbation).

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Assessment of sputum purulence:

- Patient reported sputum colour is often not reliable. Purulence can be increased in viral infections as well as bacterial infections
- Try to obtain a sputum sample to objectively assess sputum purulence where possible
- Please use the Bronko test chart to assess colour. You will find a colour chart on the Baseline CRF which you should use to match the colour of the sputum sample
- Ask the patient how much the colour of their sputum has changed from its usual colour. This is particularly pertinent when it is not possible to objectively assess their sputum.

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CRF completion and Randomisation training

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Good Clinical Practice

Good Clinical Practice should be followed at all times.

These principles require you to ensure:

- That data entered onto the CRFs is an accurate and true reflection of the patients symptoms and outcomes
- All paperwork to do with the study is locked away and only people who are named on the study delegation log should be able to have access to it.
- Passwords to the randomisation programme should not be given to anybody who is not working on the study or identified on the delegation log.

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Patient Identifiers

Please ensure that the following is completed for all CRFs:

- Today's Date
- PID – This can be obtained from the consent form
- SID – This is your own surgery unique ID and this will be provided to you before you begin recruitment
- Patient's Date of Birth
- Patient's Initials

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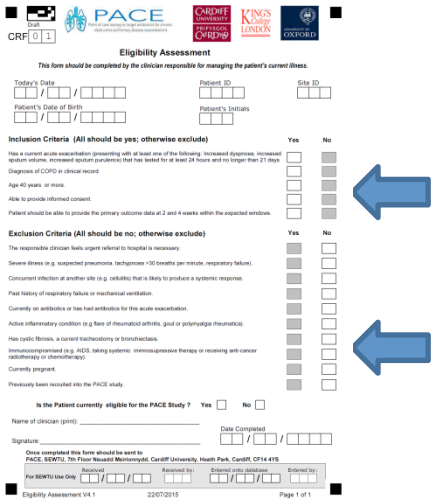
Eligibility

- In order for the participant to be part of the trial they need to meet the eligibility criteria. Eligibility must only be assessed by a GP or a Nurse practitioner
- You will need to work through the Eligibility Criteria and ensue that all of the Inclusion criteria questions are answered YES and all of the exclusion criteria questions are answered NO

- The form should be then signed and dated by the person assessing eligibility



CRF 0 1

Eligibility Assessment

This form should be completed by the clinician responsible for managing the patient's current illness.

Today's Date / / | Patient ID | Site ID

Patient's Date of Birth / / | Patient's Initials

Inclusion Criteria (All should be yes; otherwise exclude) — Yes / No

Has a current acute exacerbation (presenting with at least one of the following: increased dyspnoea, increased sputum volume, increased sputum purulence) that has lasted for at least 24 hours and no longer than 21 days

Diagnosis of COPD in clinical record

Age 40 years or more.

Able to provide informed consent.

Patient should be able to provide the primary outcome data at 2 and 4 weeks within the expected windows.

Exclusion Criteria (All should be no; otherwise exclude) — Yes / No

The responsible clinician feels urgent referral to hospital is necessary.

Severe illness (e.g. suspected pneumonia, tachypnoea >30 breaths per minute, respiratory failure).

Concurrent infection at another site (e.g. cellulitis) that is likely to produce a systemic response.

Past history of respiratory failure or mechanical ventilation.

Currently on antibiotics or has had antibiotics for this acute exacerbation.

Active inflammatory condition (e.g flare of rheumatoid arthritis, gout or polymyalgia rheumatica).

Has cystic fibrosis, a current tracheostomy or bronchiectasis.

Immunocompromised (e.g. AIDS, taking systemic immnosupressive therapy or receiving anti-cancer radiotherapy or chemotherapy).

Currently pregnant.

Previously been recruited into the PACE study.

Is the Patient currently eligible for the PACE Study ? Yes ☐ No ☐

Name of clinician (print): _____ Date Completed / /

Signature: _____

Once completed this form should be sent to:
PACE, SEWTU, 7th Floor Neuadd Meirionnydd, Cardiff University, Heath Park, Cardiff, CF14 4YS

For SEWTU Use Only | Received / / | Received by: | Entered onto database / / | Entered by:

Eligibility Assessment V4.1 22/07/2015 Page 1 of 1

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Consent

If the patient is eligible for PACE they will need to provide written informed consent

The patient will need to:

- Have time to read the Patient Information Sheet
- INITAL each box of the consent form to indicate they are happy to take part
- Write their name, signature and the date on the form

The Doctor/Nurse/healthcare assistant will need to:

- Answer any questions that the patient may have
- Inform them if they have been involved in research in the last 6 months they don't have to take part
- Write their name, signature and the date on the form

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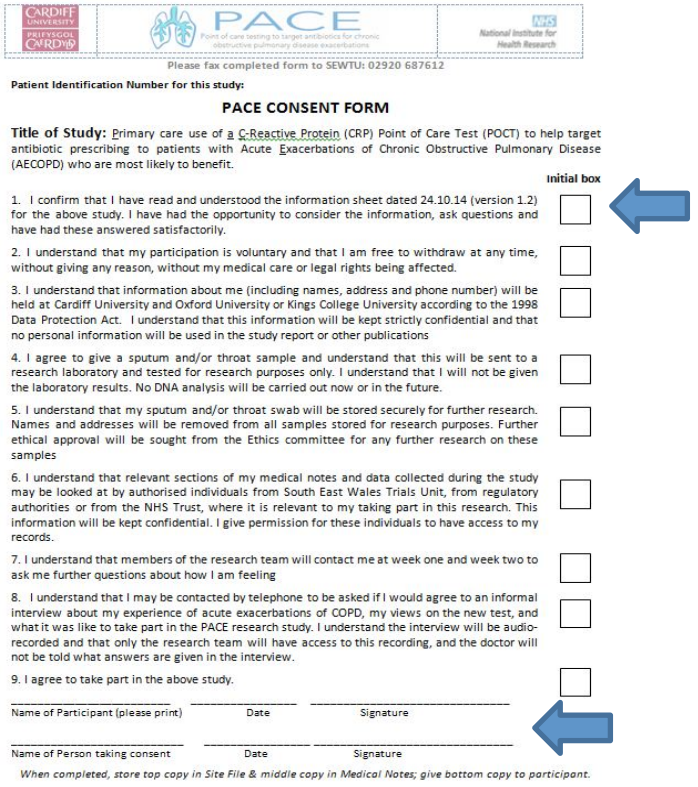
Consent

- The patient should be given a copy of the consent, one should be put in their medical notes and one in the site file

- A copy should be faxed to SEWTU as soon as possible along with the PACE contact details form



Please fax completed form to SEWTU: 02920 687612

Patient Identification Number for this study:

PACE CONSENT FORM

Title of Study: Primary care use of a C-Reactive Protein (CRP) Point of Care Test (POCT) to help target antibiotic prescribing to patients with Acute Exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD) who are most likely to benefit.

Initial box

1. I confirm that I have read and understood the information sheet dated 24.10.14 (version 1.2) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
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 information about me (including names, address and phone number) will be held at Cardiff University and Oxford University or Kings College University according to the 1998 Data Protection Act. I understand that this information will be kept strictly confidential and that no personal information will be used in the study report or other publications ☐
4. I agree to give a sputum and/or throat sample and understand that this will be sent to a research laboratory and tested for research purposes only. I understand that I will not be given the laboratory results. No DNA analysis will be carried out now or in the future. ☐
5. I understand that my sputum and/or throat swab will be stored securely for further research. Names and addresses will be removed from all samples stored for research purposes. Further ethical approval will be sought from the Ethics committee for any further research on these samples ☐
6. I understand that relevant sections of my medical notes and data collected during the study may be looked at by authorised individuals from South East Wales Trials Unit, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. This information will be kept confidential. I give permission for these individuals to have access to my records. ☐
7. I understand that members of the research team will contact me at week one and week two to ask me further questions about how I am feeling ☐
8. I understand that I may be contacted by telephone to be asked if I would agree to an informal interview about my experience of acute exacerbations of COPD, my views on the new test, and what it was like to take part in the PACE research study. I understand the interview will be audio-recorded and that only the research team will have access to this recording, and the doctor will not be told what answers are given in the interview. ☐
9. I agree to take part in the above study. ☐

Name of Participant (please print) _____ Date _____ Signature _____

Name of Person taking consent _____ Date _____ Signature _____

When completed, store top copy in Site File & middle copy in Medical Notes; give bottom copy to participant.

Baseline

- The Baseline CRF should be completed after Eligibility and consent

The Baseline CRF asks you to complete:

- How many days the patient has been suffering with this current exacerbation
- Completion of the CCQ and EQ5D outcome measures
- Medical examination
- Throat and Sputum samples – record colour of sputum sample according to bronko chart

- Once you have completed these you will need to complete the symptom questions for randomisation. These are if the patient is suffering from:

1. Shortness of breath
2. Increased sputum volume
3. Increased sputum purulence

- You will need to tick each one that applies and then total up the number that you have ticked

Randomisation

- Having assessed the 3 symptom scores you will need to randomise the patient and you do this by logging onto the PACE website www.pace-study.co.uk

- You will need to enter your log in details
- Once you are in the randomisation screen you will need to enter:

- Patient ID
- Site ID
- Patient's Date of Birth
- Confirmation of Eligibility
- Total number of symptoms (Shortness of breath, Increased sputum volume, Increased sputum purulence)
- Name of the person randomising

Once you are happy with the data entered please click submit and you will be presented with a screen showing you what arm of the trial the participant has been randomised to either the CRP arm or the Usual Care arm.

You then need to log out.

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Baseline – continued

- After randomisation you should record the details of the randomisation and the CRP result, if they have been randomised to this arm.

We then want to know about the management of the exacerbation and if you have prescribed or increased the dose of any of the following:

- Antibiotics
- Oral corticosteroids
- Inhalers which have been newly prescribed
- Inhalers which have had their dose altered
- Any other medication

- Please then sign and date the form
- Please book in the patient for their Week 4 appointment
- Inform the patient that they will receive a £10 voucher at their 4 week appointment

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Week 1 and 2 Follow Ups

- We will not be asking you to get involved with these follow up calls but we would ask that you remind the patient that they will be getting these calls.

- Please provide them with their patient pack which will contain:

1. Participant Booklet
2. Week 1 CCQ and EQ5D
3. Week 2 CCQ and EQ5D

- Please try and answer any questions that they may have regarding the follow up procedure

- The GP/nurse should provide the patient with a print out of their inhalers to aide them in writing them into their participant booklet

- The patient pack will also contain a pot for the patient to collect a sputum sample on the morning of their week 4 appointment date. They should bring this to their appointment.

- Please also ask them to bring their Participant Booklet with them to their week 4 appointment.

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Week 4

- Please book an appointment for you to see the patient at their 4 week appointment as soon as possible but preferably at the baseline appointment if this can be done

- Firstly we would like you to ask them if they have completed their 2 phone calls with our researchers. If they haven't then please complete the Week 1 / Week 2 follow up form indicating their medication use in the follow up period. Ideally this would be completed from the patient booklet

- We then want to know their medication usage in the last 2 weeks in the categories:

- Antibiotics
- Oral corticosteroids
- Inhalers
- Any other medication

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Point of care testing to target antibiotics for chronic obstructive pulmonary disease exacerbations

Week 4

- At the week 4 appointment we would like you to take a throat and sputum sample (if patient has not brought one in with them) and rate the sputum colour according to the Bronko test.

- We then would like you to record:

- Adverse Events in the last 2 weeks and rate them according to the scale
- Consultations with both primary and secondary care clinicians
- If they have had to take time off paid work
- Over the counter prescriptions
- Ask the patient to complete the CCQ and EQ5D

- Then sign and date the form

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6 Months

- At six months a note review will take place recording the patients medication and consultations with health care professionals in the last 6 months. This will be completed by NISCHR staff

- Questionnaires will be sent out to the patient for them to complete

- **If the patient dies between the four week visit and six months since being in the trial we would like you to let us know. This is so we do not inadvertently send any correspondence or questionnaires to them.**

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SAE's (SERIOUS ADVERSE EVENTS)

- An SAE form should be completed by the study site (GP/nurse) and faxed to the trial/study coordination centre for all SAEs (see below for non-reported SAEs) **within 24 hours of being made aware of the SAE.**

Serious Adverse Event (SAE): Any adverse event that:

- Results in death
- Is life-threatening
- Required hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Other medically important condition

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SAES (SERIOUS ADVERSE EVENTS)

Reporting procedures:

Non-serious AEs will not be collected

Pre-planned hospitalisation e.g. for pre-existing conditions which have not worsened or elective procedures for a pre-existing condition will not be classed as an SAE.

For all other SAE's an SAE form should be completed by the study site (GP/nurse) and faxed to the trial/study coordination centre for all SAEs within 24 hours of being made aware of the SAE.

If the patient dies between the four week visit and six months since being in the trial we would like you to let us know. This is so we do not inadvertently send any correspondence or questionnaires to them.

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Return of forms and samples:

- Fax consent form and contacts CRF to SEWTU as soon as possible
- Return eligibility, baseline and week 4 CRFs to SEWTU in pre-paid envelopes provided
- Return the baseline and week 4 questionnaires to SEWTU in pre-paid envelopes provided
- Post all samples to the SACU microbiology laboratory in transport bags provided

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GP Agreement

- Schedule 1 : Sign and complete the PI Declaration and return the GP Site Agreement to SEWTU
- Schedule 2 : Sign the Terms of Use relating to the Afinion Analyzer set out in this GP Site Agreement
- Delegation Log – Detail everyone who is will be working on the study, obtain their signature, detail what responsibilities that they will have and then each person will need to be signed off by the PI.
- Return to SEWTU as soon as possible

www.pace-study.co.uk

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