PACE Study Protocol

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

Protocol VERSION 5.0, 15.03.2016

Sponsor:	Cardiff University, 30-36 Newport Road, Cardiff, CF24 0DE
Sponsor ref:	SPON1178-12
Funder:	NIHR HTA
Funder ref:	12/33/12
REC ref:	14/WA/1106
ISRCTN ref:	ISRCTN24346473

This protocol has been authorised by:

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V5.0 15.03.16

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General Information This protocol describes the PACE Study and provides information about the procedures for entering participants into the Study. The protocol should not be used as a guide, or as an aide-memoire for the treatment/care of other patients/participants. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the study, but centres entering patients/participants for the first time are advised to contact the South East Wales Trials Unit (SEWTU) in Cardiff to confirm that they have the most up-to-date version of the protocol in their possession. Problems relating to the Study should be referred, in the first instance, to SEWTU.

Compliance This study will adhere to the conditions and principles outlined in the ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95). It will be conducted in compliance with the protocol, the Research Governance Framework for Health and Social Care (Welsh Assembly Government November 2001 and Department of Health 2nd July 2005), the Data Protection Act 1998, and other regulatory requirements as appropriate.

Funding The PACE Study is being funded by NIHR Health Technology Assessment Board.

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Please contact the Trial Manager for general queries and supply of Trial documentation

Randomisations:

Randomisation
To randomise a patient log on to http://www.pace-study.co.uk/
For the telephone back up randomisation call 07814 301606

Clinical queries:

Clinical queries
All clinical queries should be directed to the Trial/Study Manager who will direct the query to the most appropriate clinical person.

Serious Adverse Events:

SAE reporting
Where the adverse event meets one of the serious categories an SAE form should be completed by the responsible clinician and faxed to the PACE Trial/Study Manager within 24 hours upon becoming aware of the event (See sections 16 for more details).

Table of Contents

Glossary of abbreviations

A&E	Accident and Emergency
AE	Adverse Event
AECOPD	Acute Exacerbation of Chronic Obstructive Pulmonary Disease
AMR	Antimicrobial Resistance
AUC	Area Under the Curve
CA	Competent Authority
CACE	Complier Average Causal Effect
CCQ	Clinical COPD Questionnaire
CF	Consent Form
CI	Chief Investigator
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRP	C-Reactive Protein
CRQ-SAS	Chronic Respiratory Questionnaire Self-Administered Standardised
CU	Cardiff University
CUA	Cost Utility Analysis
ICH	International Conference on Harmonization
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	General Practitioner
HTA	Health Technology Assessment
IC	Informed consent
IDMC	Independent Data Monitoring Committee
ISRCTN	International Standard Randomised Controlled Trial Number
HB	Health Board
HR QoL	Health Related Quality of Life

LRTI	Lower Respiratory Tract Infection
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NISCHR	National Institute for Social Care & Health Research
NISCHR-CRC	National Institute for Social Care and Health Research Clinical Research Collaboration
PI	Principal Investigator
PIS	Patient Information Sheet
POCT	Point of Care Test
QALY	Quality-adjusted Life Years
QL (QoL)	Quality of Life
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SEWTU	South East Wales Trials Unit
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

1 Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	1.1	02.09.2014	J Nuttall	Minor changes and addition further clarification regarding the future use of the samples and disposal of the capillary tube for the finger prick
2	2.0	29.10.14	J Bates	Change of primary outcome measure from CRQ-SAS at two week follow-up to CCQ at two-week follow-up. Addition of CRQ-SAS at six month follow-up Inclusion/exclusion criteria –re-phrasing and some additions Expansion on qualitative evaluation process Alteration to microbiological analysis Change to patient information sheet to add that we will collect participants address
3	3.0	27.01.15	J Bates	Clarifying and defining which staff at site can assess patient eligibility. Change of wording in one of the inclusion criteria from: Spirometry confirmed (post bronchodilator FEV1/FVC <0.7) mild, moderate or severe COPD (GOLD Grade 1, 2 & 3) To: Spirometry confirmed mild, moderate or severe (GOLD Grade 1, 2 or 3) COPD (FEV1≥ 30% predicted). Clarifying that the primary objective and primary outcome is antibiotic use for AECOPD, and table 4 has been changed from antibiotic prescribing to antibiotic

				consumption. All cause antibiotic consumption during the first four weeks has been added to the secondary objectives, outcomes and analysis sections. EQ-5D has been added to the 6 month postal follow-up. The CRP guidance has been corrected to the following categories: <20, 20-40, >40 Clarifying the safety reporting procedures. New investigator (Carl Llor) and new administrator (Christian Barlow) has been added.
4	V 4.0	08.06.15	J Bates	Clarify secondary outcome is prevalence of resistant bacteria is in throat swab Change from the EQ5D-3L to the EQ5D-5L Inclusion/exclusion criteria –re-phrasing and some additions Clarification that the randomisation says Usual Care not No POCT Amend typo on back up randomisation phone number Amend 4 week follow up window from -3 days to +14 days from +7 days
5	V4.1	01.10.15	J Bates	Clarification that Alere will provide training only to those practices using an Alere CRP machine. Demographic data, FEV1, clinical history and smoking status no longer collected at baseline. Clarification around the contacting of patients for their 6 month questionnaire data – telephone and postal.

				Qualitative Interview topic guides – improved wording and flow – but still focused on the same topics (views on the CRP test, research processes and management of COPD)
6	V5.0	15.03.16	J Bates	6 month note review will also include a 12 month note review of antibiotics prescribed prior to the baseline appointment. The time frame within which the qualitative interviews with participants can be carried has been increased from 2 weeks (post 4 week follow-up date) to 4 weeks.

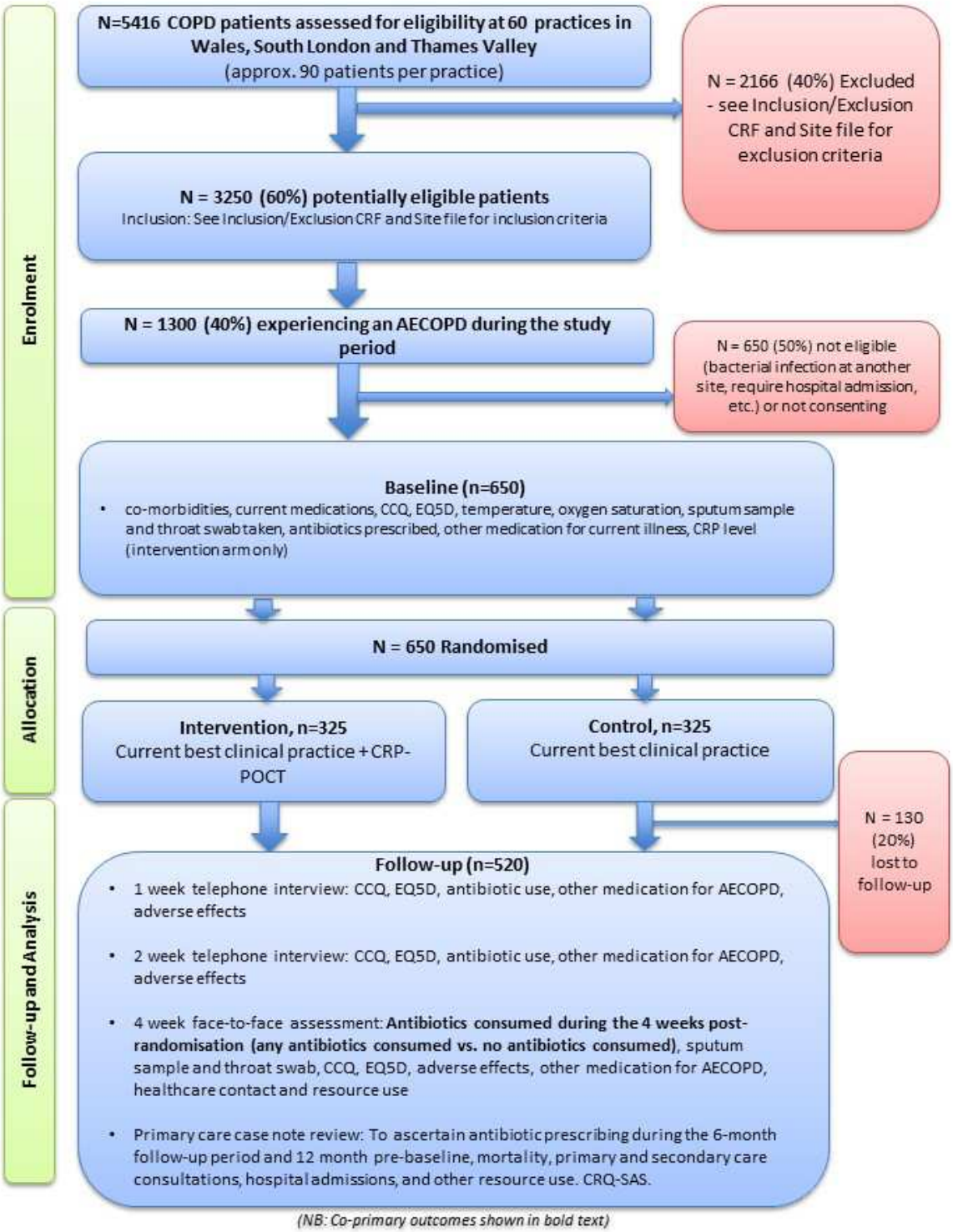
2 Synopsis

Acronym	PACE Study
Title	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
Internal ref. no.	SPON1178-12
Trial design	Two-arm individually (1:1 ratio) randomised controlled trial
Trial participants	Patients on practice COPD registers/diagnosed with COPD consulting with an AECOPD in primary care
Planned sample size	650
Follow-up duration	6 months
Planned trial/study period	37 months
Primary objective	To determine whether the addition of a CRP POCT (with training on test use and interpretation) to current best practice based on NICE guideline for managing an AECOPD leads to a reduction in antibiotic consumption for the exacerbation within four weeks post index consultation without negatively impacting on COPD health status (measured at two weeks post index consultation), compared with current best practice alone.
Secondary objectives	To assess the effect of using a CRP POCT for AECOPD in primary care on: 1. Prevalence of resistant bacteria in throat swab and sputum samples at 4 weeks 2. COPD health status over time (weeks 1, 2 and 4) 3. Health utility, measured using the EQ-5D-5L at 1, 2 and 4 weeks and at 6 months 4. All cause antibiotic consumption during the first four weeks 5. Antibiotic prescribing at the index consultation 6. Use of other COPD treatments including oral steroids during the first four weeks 7. Adverse effects from antibiotics and other medication prescribed for their AECOPD during the first four weeks 8. Primary and secondary care consultations (including out of hours, A&E visits and hospitalisations) during the

	subsequent 6 months 9. Costs and cost-effectiveness from a health service perspective 10. Incidence of pneumonia during the first 4 weeks and first 6 months post randomisation 11. Disease-specific HRQoL (CRQ-SAS) at 6 months post-randomisation
Primary endpoint	co-primary: 1. Consumption of antibiotic in the 4 weeks post randomisation for AECOPD. 2. Clinical COPD Questionnaire (CCQ) at two weeks post-randomisation.
Interventions	CRP POCT instrument, training in its use, and web-based training in interpreting the results.

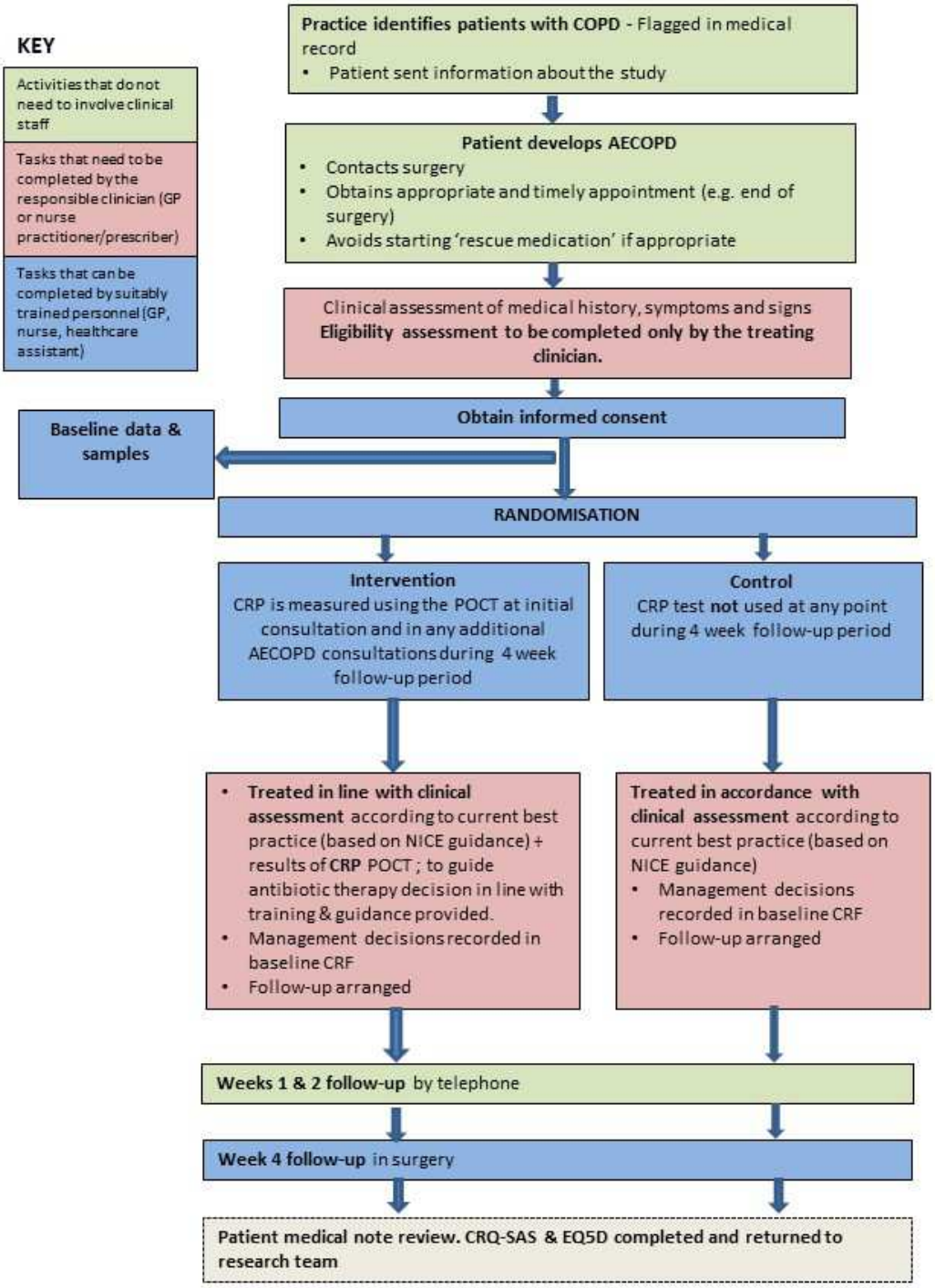
3 Trial summary & schema

3.1 Trial schema (projected numbers)



(NB: Co-primary outcomes shown in bold text)

3.2 Participant flow diagram



3.3 Trial summary

This will be a multicentre randomised controlled trial (RCT) involving general practices based in Wales, Oxford and London. We will conduct a two-arm individually randomised RCT including 650 patients with a diagnosis of COPD (e.g. on COPD register consulting with an acute exacerbation of COPD (AECOPD) in primary care. Eligible patients will be randomised either to management according to best current practice (NICE guideline-informed) alone (control) or to best current practice with the addition of a CRP POCT to guide decisions about initial antibiotic treatment at the index consultation. We will assess whether the addition of the CRP POCT results in better targeting of antibiotic treatment, thereby reducing the overall consumption of antibiotics for COPD without compromising COPD health status. Our co-primary outcomes will be consumption of an antibiotic at any point during the four weeks following randomisation for AECOPD and COPD health status at follow up two weeks after randomisation assessed using the Clinical COPD Questionnaire (CCQ). The trial will be designed to assess a number of clinical, patient-centred, and health service resource-related secondary outcomes. Basic anonymous clinical and demographic data will be collected on all eligible patients, whether they decide to participate or not, so that we can assess reach and determine how representative the trial participants are of the UK population that presents in primary care with AECOPD. Implementation of the POCT, adherence to the prescribing guidance provided, and acceptability of the intervention to clinicians and patients will be monitored. Analysis will be completed on an intention-to-treat basis, but will include a CACE analysis, and we will measure major clinical secondary outcomes (including incidence of pneumonia and hospitalisation).

4 Introduction

4.1 Background

Better targeting of antibiotics for acute exacerbations of chronic obstructive pulmonary disease (COPD) represents a major opportunity for antimicrobial stewardship. Over 80% of all antibiotics are prescribed in primary care (1) and antibiotic prescribing in primary care is once again increasing. AECOPD accounts for over two million antibiotic prescriptions each year in the UK. Cohort studies of patients recruited in secondary care (which may not be representative of primary care but is the best data that we have) suggest that COPD patients in the UK will suffer between 2.5 and 3 AECOPD per year (2). Over 70% of patients presenting with AECOPD in primary care are prescribed an antibiotic, accounting for 4.6% of all antibacterial prescriptions every year (3). COPD patients are an important and expanding group who are at risk of significant mortality, morbidity and hospitalisation, and as such are more likely to be prescribed broad-spectrum antibiotics. However, many AECOPD are triggered by non-bacterial causes. AECOPD are often triggered by viral infections and environmental stresses such as common pollutants or weather. It has been estimated that approximately 70% of AECOPD are triggered by an infection and 30% being caused by other environmental factors. Of the 70% that are triggered by an infection, potential pathogenic bacteria are only isolated in 20-58%, whilst pathogenic respiratory viruses can be detected in approximately 50% (4-6). Current antibiotic prescribing recommendations for GPs are generally based on symptoms alone (Anthonisen criteria). However, these have insufficient diagnostic accuracy to predict which patients can safely be managed without antibiotics. Research from our team (7) and systematic reviews (8) suggest that many patients with AECOPD in primary care do not benefit from antibiotic treatment. Overuse of antibiotics drives increased antimicrobial resistance (9). COPD is no exception: infections with antibiotic resistant *S. pneumoniae* in patients with chronic COPD are associated with antibiotic exposure (10). A meta-analysis of seven studies of respiratory tract bacteria that included 2605 participants showed that the pooled odds ratio (OR) for resistance was 2.4 (1.4 to 3.9) within two months of antibiotic treatment, and 2.4 (1.3 to 4.5) within 12 months (1). Therefore, unnecessary use of antibiotics for AECOPD not only contributes to the increasingly pressing public health threat of antibiotic resistance, it also poses a risk for the individual, and may increase the risk of subsequent exacerbations and disease progression. Moreover, the indiscriminate use of antibiotics in patients with COPD is particularly high risk because these individuals' respiratory tracts are frequently colonised with potential pathogens (11). Antibiotic exposure in these individuals is therefore likely to promote resistance in pathogenic organisms, which are likely to pose a greater risk for the individual and society as a whole. Unnecessary antibiotics also increase the risk of patient side effects, wastes money and undermines self-care (12).

4.2 Rationale for current Trial

A Cochrane systematic review of the use of antibiotics in the management of exacerbations of COPD, published in 2012, included 16 trials with n=2068 participants (8). The review reported that evidence was inconsistent and found insufficient evidence to guide antibiotic prescribing decisions in primary care (8). Their meta-analysis of trials of currently available antibiotics found no evidence of benefit in outpatients (and low

quality evidence of a small reduction in the risk of treatment failure when all outpatient studies were included). The authors called for: *'research into the clinical signs and biomarkers to help identify patients who benefit from antibiotics and patients who experience no benefit, and in whom downsides of antibiotics (side effects, cost, multi-resistance) could be avoided'* (p. 2, 8). POCT biomarker tests have not been evaluated to stratify treatment for patients with AECPOD in primary are.

C-reactive protein (CRP) is an acute phase protein found in the blood. Levels rise in response to inflammation. The serum level of CRP increases rapidly during infections, particularly in severe bacterial infections. A prospective evaluation of 36 biomarkers found that CRP was the most selective biomarker to confirm AECOPD and in combination with Anthonisen criteria produced an AUC of 0.88 (95% CI; 0.82-0.93) (13). High serum CRP is correlated with sputum purulence and increased serum leukocyte counts, and serum CRP is higher in the presence of bacterial infection (14, 15). CRP rises in patients with AECOPD and is correlated with Anthonisen score and the degree of airflow limitation in hospitalised patients (16, 17). CRP levels are especially raised in the presence of bacterial infection (18), and the treatment effect of antibiotics increases as the value of CRP increases (19). A CRP value above 50 mg/L (Mean CRP of 97mg/L, 95% CI (49–145)) in hospitalised patients with AECOPD is associated with Pneumonia and they are likely to benefit from antibiotics) (17). CRP measurement independently distinguished between pneumonia and exacerbations in another study of hospitalised patients (cut-off value of 48mg/L with sensitivity of 91% and specificity of 93%) (20). In a randomised controlled trial we conducted in patients with AECOPD in primary care we found no difference in clinical cure between antibiotics and placebo in those with a CRP<40 (risk ratio (RR) for clinical failure = 0.72 (95%CI 0.28 to 1.82) p=0.484). Our guidance takes a conservative approach and includes cut points of <20 and <40 with greater emphasis on not prescribing for those in the lower category.

The majority of patients consulting GPs with AECOPD have CRP values below 10 mg/L, and as long as the exacerbation has been present for at least 24 hours, the risk of a serious bacterial infection is negligible when the CRP value is so low. In an as yet unpublished study we found that 51% of confirmed COPD patients experiencing an exacerbation had a CRP < 10 mg/L. Our recent placebo-controlled trial of antibiotics for AECOPD in primary care (14) found marginal benefit from antibiotic treatment in patients with only one or two Anthonisen criteria. Using Anthonisen criteria to predict benefit from antibiotic treatment produced an area under the curve (AUC) of 0.708 (95% CI 0.616 – 0.801). Adding CRP increased this to an AUC of 0.842 (95% CI 0.76 – 0.924). Based on these data we anticipate that using a CRP test alongside clinical assessment will make it possible to safely reduce the antibiotic prescription rate for this condition to around 45%.

CRP POCTs are widely available and are already commonly used to help guide antibiotic prescribing decisions, including for LRTI and AECOPD in primary care in a number of European countries (mostly Scandinavian). We have previously led or contributed to two trials (21, 22) evaluating the use of a CRP POCT to help target antibiotic treatment for lower respiratory tract infections in primary care. The antibiotic prescription rates for those with lower respiratory infections were 53% and 68% in the usual care groups. ***These studies demonstrated that use of the test (with training) resulted in 22% and 29% reductions in antibiotic prescribing***, and that CRP is cost effective in reducing antibiotic prescribing for LRTI at no, or low willingness to pay (23, 24).

However, CRP testing in conjunction with clinical examination has not yet been evaluated for AECOPD in primary care. Now that better and more rapid CRP POCTs are available (25), there is real potential for this technology to be widely used in primary care to help contain antibiotic resistance. PACE seeks to establish whether a CRP POCT can safely and cost-effectively be used to target antibiotic treatment for AECOPD in primary care to those that are most likely to benefit, so that overall antibiotic use is decreased.

5 Trial objective

5.1 Primary objective

To determine whether the addition of a CRP POCT (with training on test use and interpretation) to current best practice based on NICE guideline for managing an AECOPD leads to a reduction in antibiotic consumption for AECOPD without negatively impacting on COPD health status, compared with current best practice alone. To meet this objective, we will assess:

1. Antibiotic consumption (any consumption of antibiotics for AECOPD vs. no consumption of antibiotics for AECOPD) over the first four weeks following randomisation. Actual consumption (rather than prescribing or dispensing) is the driver of AMR, and a four-week window will allow us to capture consumption of both antibiotics prescribed at the initial consultation and those that are related to the AECOPD episode in question, but are obtained or started at a later date.
2. Recovery in terms of COPD health status, which will be assessed at two weeks post-randomisation using the CCQ. Two-weeks is the time when most patients will have recovered (in terms of improvement in health status and physiological parameters) and therefore the point at which a difference would be most indicative of a delayed recovery.

5.2 Secondary objectives

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

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

6 Trial design

Two-arm individually (1:1 ratio) randomised controlled trial. Patients with AECOPD randomised to be managed by current best practice (NICE guideline informed) alone or with the addition of a CRP POCT and protocol-based training in test use and interpretation to guide decisions about the use of antibiotic treatment for AECOPD.

Co-primary outcomes (antibiotic consumption for AECOPD within four weeks post-randomisation and COPD health status two weeks-post randomisation) will be used to answer the primary research question of the study. Between-group differences in antibiotic consumption will be investigated for superiority, while differences in COPD health status will be investigated for non-inferiority.

7 Centre and Investigator selection

The first winter period will comprise an internal pilot in 10 practices in Wales (see section 11). During the second winter period, we will have at least 60 practices (approximately 20 in each of the three regions: Wales, Thames Valley and South London). We will monitor recruitment closely and if necessary replace slow recruiting practices and/or expand to new practices/regions

The following regional networks will support the three centres in site set up, recruitment and follow up:

- Wales: Wales wide National Institute for Social Care and Health Research Clinical Research Collaboration (NISCHR-CRC) and the new Primary Care Research Incentive Scheme.
- South London: The Greater London Primary Care Research Network (PCRN-GL), which currently works with more than 300 practices.
- Thames Valley: The Thames Valley Primary Care Research Network (PCRN).

We will aim to recruit practices with an average patient list size of >5000. However, smaller practices with a significant number of COPD patients and a good track record of recruiting patients into research studies will also be considered.

Before any Centre can begin recruitment a Principal Investigator at each Centre must be identified. The following documents must be in place and copies sent to the PACE Trial Manager (see contact details on page 5):

- The approval letter from the Centre's R&D Department, following submission of the Site Specific Information (SSI) form (where required)
- A signed Study Agreement (PI and sponsor signature)
- Completed Signature List and Roles and Responsibilities document
- Completed contacts list of all site personnel working on the Study
- Signed confirmation that the GPs have undergone the algorithm training package

Upon receipt of all the above documents, the PACE Trial Manager will send a confirmation letter to the Principal Investigator detailing that the centre is now ready to recruit patients into the study. This letter must be filed in each centre's Site File. Along with this confirmation letter, the centre should receive their trial supplies and a study pack holding all the documents required to recruit a patient into the PACE Trial.

8 Participant selection

Patients are eligible for the trial if they meet all of the following inclusion criteria and none of the exclusion criteria. All queries about patient eligibility should be directed to the PACE Trial Manager before randomisation.

8.1 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

8.2 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

9 Recruitment and randomisation

9.1 Number of participants

We aim to recruit 650 participants from general practices based in three centres; Wales, Thames Valley and South London.

9.2 Recruitment process

9.2.1 Identifying participants

Potential participants will be recruited from primary care across the three centres. Recruitment strategies may differ between centres depending on local geographic and organisational factors.

Participating practices will conduct a search of their patient electronic records based on their COPD register and identify all potentially eligible patients at the start of the study. These patients will be 'flagged' in their general practice clinical record using pre-specified Read codes in order to allow easy identification of patients when they contact the surgery who could be eligible to participate. .

Sites will have the option of using Docmail, where appropriate, to send relevant patients a letter informing them about the study (on practice headed paper), a study summary sheet and a participant information sheet (PIS). Also included will be a patient card with "Potentially eligible for PACE Study" This will allow potential participants the opportunity to consider whether they would like to participate should they develop an AECOPD during the recruitment period. Patients will be encouraged to identify themselves with the aid of the card, to the practice as having a suspected AECOPD, and where appropriate, consult before taking any oral antibiotics or oral steroids that they have at home ('rescue medications'). Study posters will be used in surgery waiting areas to inform patients about the study.

Participating clinicians will be asked to approach eligible patients opportunistically in routine surgery sessions as well as patients that are booked into special PACE appointments. Patients will only be recruited once into PACE. Clinicians will be provided with pre-prepared study packs containing information and consent forms for patients.

9.3 Assessment of participant eligibility

The doctor or nurse responsible for managing the patient's current illness must complete the eligibility assessment.

9.4 Informed consent

All participants will be fully informed about the trial through the Participant Information Sheet (PIS), supplemented by verbal explanations from practice nurses or GPs.
Informed consent to participate in the trial (and baseline data collection and randomisation) will be obtained by the GP or nurse that the patient first consults with or by an appropriately trained nurse in the practice. In order to facilitate conduct of the study into busy general practice workflows, we will permit practices to share tasks between appropriately trained clinical staff. As such, some practices will have a nurse (or nurses) trained in explaining the study to potential participants, obtaining informed consent, collecting baseline data, randomisation, and conducting the POCT test (if relevant). In these practices, if the patient initially consults with another clinician in the

practice, that clinician will have the option of discussing the study with the patient and then asking them if they are happy to see the practice nurse to discuss the option of participating in the study in more details. For all participants, signed informed consent will be obtained according to Good Clinical Practice (GCP). Potential participants will be given sufficient time to accept or decline participation and will be given the opportunity to ask questions.

Once consented to the study participants will be allocated a unique trial number (participant ID), which will be the primary identifier for all participants in the trial.

9.5 Randomisation

Participants will be remotely randomised using an online computerised randomisation system created by SEWTU which will be operational 24 hours a day. A 8.30am -6.30pm telephone back up will be available for use if the online system does not work or the GP Practice has problems accessing the online site.

Randomisation can only be performed after the participant has signed the consent form.

For online randomisation: Participants will be randomised to either POCT test or usual care.

For Telephone randomisation: A randomisation form must be completed before telephoning the randomisation line. Participants will be randomised to either POCT test or usual care.

Randomisation
To randomise a patient log on to http://www.pace-study.co.uk
For the telephone back up randomisation call 07814 301606

9.6 Screening logs

Sites will be asked to collect a screening log of anonymous data on all ineligible and eligible but not consented/not approached, so that any biases from differential recruitment will be detected. Reasons for not being invited or for declining participation will be recorded. The screening log should be sent to the PACE Trial Manager every month (see section 19 for further detail on data monitoring/quality assurance).

10 Withdrawal & loss to follow-up

Participants have the right to withdraw consent for participation in any aspect of the PACE Trial at any time. The participant's care will not be affected at any time by declining to participate or withdrawing from the Trial.

If a participant initially consents but subsequently withdraws from the trial, a clear distinction must be made as to what aspect of the trial the participant is withdrawing from. These aspects could be:

1. Withdrawal from trial intervention

2. Withdrawal from further trial/study follow-up

3. Withdrawal from entire trial/study and does not want data to be used.

In all instances participants who consent and subsequently withdraw should complete a withdrawal form (see Withdrawal Form in trial pack) or the withdrawal form should be completed on the participant's behalf by the researcher/clinician based on information provided by the participant. This withdrawal form should be sent to the PACE Trial Manager via fax (02920 687512). Any queries relating to potential withdrawal of a participant should be forwarded to the Trial Manager immediately via phone, email or fax.

We will make every effort to reduce loss to follow-up using the methods listed below:

i. We will emphasise the importance of getting follow-up data to all participants at baseline and the different follow-up assessment points.

ii. Unless they have explicitly requested otherwise, all participants will be invited to complete follow-up questionnaires and attend follow-up appointments.

iii. We will arrange mutually acceptable dates for the one and two-week telephone interviews, and four-week face-to-face assessment, at the baseline visit.

iv. We will obtain telephone contact details of all participants at baseline. We will also ask participants about times of the day that would be most suitable for the one and two-week telephone interviews.

v. For the telephone interviews, up to three attempts will be made to contact a participant on the scheduled date of their interview. Where contact has been unsuccessful following these attempts, three attempts will be made to contact the participant each subsequent day for up to:

a. two working days for the one-week telephone interview;

b. seven working days for the two-week interview.

11 Internal Pilot

An internal pilot phase will be conducted during the first winter period with approximately 10 practices in Wales. The primary aims of the internal pilot are to assess the recruitment rate, adherence to intervention allocation and the proportion of patients in whom we are able to measure both co-primary outcomes. Secondary aims are to assess the proportion of eligible patients recruited, and measurement of secondary outcomes. The study funder (NIHR HTA Programme) will assess the study against these criteria at the end of the internal pilot.

Qualitative evaluation during the internal pilot

A qualitative evaluation will be included in the internal pilot. The aims of this qualitative evaluation will be to:

1. Identify barriers and facilitators to use of the CRP POCT for both clinicians and study participants Identify other barriers and facilitators to participation in the study for both clinicians and study participants
2. Identify themes relating to both positive and negative experiences of taking part in the study for both clinicians and study participants

Internal pilot phase qualitative evaluation method

Semi-structured interviews will be carried out with members of the primary care teams and patients to gather in-depth information on their experience of participating in the study. These will be conducted face-to-face or by telephone.

Participants and recruitment

Qualitative evaluation will be conducted with approximately 10 patients and 10 clinicians during the pilot study. For the clinicians, we will write to participating general practices in Wales with information about the qualitative interviews. We will then telephone the practices to identify individuals who would like to take part and arrange a convenient time to conduct the interviews. Members of the primary care team will provide written consent when interviews are carried out face to face. Consent will be given verbally for telephone interviews; the researcher will read the same statements that are included in the written consent form, and ask the clinician whether they agree with each of these. Verbal consent will be audio-recorded. We anticipate interviewing 2-3 members of the team in 3-4 practices. We will ensure that the sample includes a cross section of individuals who have been involved with use of the CRP POCT and completion of data collection forms (at least five), as well as including at least three GPs in these interviews.

We will also interview 10 participating patients. The patient consent form for participation in the main study will include consent for the qualitative interviews. Patients will be selected on the basis of obtaining participants from a range of practices (to include patients from at least five different practices), and patients randomised to both CRP POCT and usual care trial arms (approximately five patients from each trial arm). The patients selected will be telephoned within two weeks of their four week follow-up assessment to invite them to take part in an interview. If they accept, a convenient time will be arranged for the researcher to telephone them to carry out the interview.

We will keep a log of clinicians and patients who have been invited to take part in an interview so that a response rate can be estimated, and anonymised information relating

to the characteristics of responders and non-responders can be assessed for potential sampling bias.

Procedure for the pilot phase qualitative evaluation

A researcher trained in qualitative interviewing will conduct the interviews in a quiet location in the practices or over the telephone as appropriate. They will use a flexible topic guide comprised of key questions and prompts to ensure that essential information is gathered, while allowing the interviewer flexibility to seek clarification or explore emerging themes in more depth where required. It is anticipated that the interviews will be approximately 30 minutes in duration.

Patients who have agreed to be contacted for an interview will be telephoned by the research team within two weeks of their four week follow-up appointment at their GP practice (i.e. 4-6 weeks from their initial consultation). This is to ensure that the qualitative data collection does not have an impact on the primary outcome data for the trial, while allowing reasonable recall of the consultation.

Clinicians will be contacted towards the end of the recruitment period for the internal pilot to allow them to gain sufficient experience of using the CRP POCT, while minimising the potential impact on practice of carrying out the interviews during the recruitment period.

Analysis of the pilot phase qualitative evaluation

Interviews will be audio recorded and transcribed. Data will be analysed thematically. A coding framework will be developed based on using both the pre-defined themes included in the topic guide (to ensure the pre-defined study objectives are met) and new themes emerging from the data. A sample (20%) of the interviews will be dual coded for validation purposes. NVivo qualitative analysis software will be used to assist coding.

12 Intervention

PACE will assess use of a C-reactive protein (CRP) point-of-care test (POCT) to guide antibiotic treatment decisions for patients presenting in primary care with AECOPD. Patients randomised to the intervention arm will have a CRP test at every consultation for AECOPD that occurs in the four weeks following randomisation. Control patients will not have a CRP test (as part of this study) at any time during their participation.

The CRP POCT is developed by Alere (http://www.afinion.net/tests/afinion_CRP). The Alere Afinion CRP test requires 1.5µl of capillary blood (finger prick) and takes <4 minutes to provide a quantitative result. The capillary tube will be disposed of according to local practices and no blood will be kept. Other validated CE marked devices giving a quantitative CRP result and requiring a similar volume of blood from a finger prick will also be eligible for use in the study.

12.1 Intervention Arm

General practitioners will use the results of the CRP test to help guide their antibiotic prescribing decision. Participating clinicians will be provided with study specific training, which will include guidance on interpreting CRP test results in the context of AECOPD, and a laminated guidance sheet (table 2).

TABLE 2

CRP Guidance:
The decision to prescribe antibiotics or not has to 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
Measurement of CRP can aid decision-making but is not meant to replace clinical assessment. Patients with the following features are likely to be at increased risk of complications: • Severe COPD (GOLD grade 3) • Past history of severe exacerbations (requiring hospitalisation) • Significant co-morbidities (e.g. heart failure, poorly controlled diabetes, lung cancer)
Sputum purulence is currently the best clinical predictor of bacterial infection. **However:** • Patient reported sputum colour is generally not reliable. • Purulence can be increased in viral infections as well as bacterial infections • Try and obtain a sputum sample in order to objectively assess sputum purulence where possible. • 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.	
CRP Measurement:	
CRP < 20	Antibiotics are unlikely to be beneficial and usually should not be prescribed.
CRP 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.
CRP > 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).

12.2 Control Arm

Patients randomised to the control arm will receive 'current best practice'. All participating clinicians will receive training at the start of the study and be able to re-access the training at any point in the study. The training will include a brief summary of NICE and GOLD guidance in relation to the management of AECOPD. No other specific guidance or instructions will be given to clinicians in relation to the management of patients randomised to usual care. Therefore, the only difference between the two arms will be that patients in the usual care arm will not have their management guided by use of the CRP POCT.

12.3 Adherence to use of intervention

Adherence to the use of the POCT will be monitored via patient completed telephone questionnaire as well as through monitoring the cartridge log number used with the CRF questions on the CRP test.

13 Outcome measures

13.1 Primary outcome measures

- Antibiotic consumption at any point during the four weeks post-randomisation for AECOPD, measured using telephone interviews at one-week and two-weeks and face-to-face interview at four-weeks.
- COPD health status measured by the Clinical COPD Questionnaire (CCQ)(26) via telephone interview at two-weeks. The CCQ is a patient-centred health status measure that has been well validated and is widely used in patients with COPD(27)

13.2 Secondary outcome measures

- Prevalence of significant pathogenic bacteria (including S*. pneumoniae, H. spp and Enterobacteriaceae)* cultured from sputum at baseline and 4 weeks;
- Prevalence of antibiotic resistant commensal organisms cultured from throat swabs at 4 weeks;
- COPD health status over time measured using the CCQ (measured at weeks 1, 2 and 4);
- Health utility measured using the EuroQol-5D (EQ-5D-5L) (measured at weeks 1, 2 and 4 and at month 6);
- All cause antibiotic consumption during the first four weeks
- Antibiotic prescribing at the index consultation;
- Use of other COPD treatments including oral steroids (measured at weeks 1, 2 and 4);
- Adverse effects potentially attributable to antibiotics prescribed for their exacerbation (nausea, vomiting, diarrhoea, thrush, and rash) (measured at weeks 1, 2 and 4);
- Primary and secondary care consultations, including hospitalisations (measured at week 4 and month 6);
- Costs (total NHS cost) and cost-effectiveness (measured at month 6);
- Incidence of pneumonia (measured by patient and GP report at week 4 and month 6).
- Disease-specific health-related quality of life over time measured using CRQ-SAS (measured at month 6)

13.3 Process Evaluation of the main study

- Qualitative interviews with up to 20 patients in the active intervention group and up to 20 clinicians to assess how the intervention was implemented, acceptability, and contextual factors.
- Records will be kept by clinicians of reasons for overriding the guidance on antibiotic prescribing according to CRP levels.
- Clinicians will keep a record of the number of test cartridges from the POCT system used for training/familiarisation of clinical staff, successfully used, discarded due to errors during sampling, discarded due to errors during testing, or used for other purposes.
- Any technical difficulties with the test equipment.

Qualitative process evaluation participants and recruitment

The aim of the qualitative element of the process evaluation is to understand how the intervention was used and identify possible mechanisms for any observed effects. Specific objectives are to:

1. Understand patient perspectives on the use of the CRP POCT to help guide the management of AECOPD
2. Understand clinician perspectives on the use of the CRP POCT to help guide the management of AECOPD
3. Gain an understanding of the barriers and facilitators to using the CRP POCT, as perceived by primary care clinicians and participating patients
4. To provide contextual information that can inform further implementation and roll-out (if appropriate), including:
    a. General views of primary care team members on conducting POCT testing for AECOPD in primary care
    b. Patient perspectives on the routine management of AECOPD, including the use of antibiotics
    c. Primary care clinicians' views on the challenges involved in the routine management of AECOPD

Method for qualitative process evaluation

Semi-structured interviews will be carried out with patients and clinicians by telephone to gather in-depth information about the acceptability and implementation of the CRP POCT test.

Participants

We will interview 20 patients from the CRP-POCT trial arm and 20 primary care clinicians from participating practices.

For the clinician interviews, we will write to participating general practices with information about the qualitative interviews. We will then telephone the practices to identify individuals who would like to take part and arrange a convenient time to conduct the interviews. Consent will be given verbally for telephone interviews; the researcher will read the same statements that are provided on the written consent form, and ask the clinician whether they agree with each of these. Verbal consent will be audio-recorded. We will ensure that we sample a cross section of individuals from each of the recruitment regions (Wales, Thames Valley and South London – at least five from each region), and include both GPs (at least five) and other members of the primary care team (at least five) who have been involved with using the CRP POCT test in the sample.

The patient consent form for participation in the main study will include consent for the qualitative interviews. Patients will be selected on the basis of obtaining participants from a range of practices in each region (to include patients from at least five different practices in each area), and to represent patients who were or were not prescribed antibiotics during the index consultation (at least eight with and without antibiotics prescribed). The patients selected will be telephoned within two weeks of their four week follow-up assessment to invite them to take part in an interview. If they accept, a convenient time will be arranged for the researcher to telephone them to carry out the interview.

We will keep a log of clinicians and patients who have been invited to take part in an interview so that a response rate can be estimated, and anonymised information relating to the characteristics of responders and non-responders can be assessed for potential sampling bias.

Procedure

Semi-structured interviews will be carried out over the telephone by a researcher who has received training in qualitative data collection. Flexible topic guides will be used for the clinician and patient interviews. The interviews will be audio-recorded, and will be approximately 30 minutes in duration.

Patients who have agreed to be contacted for an interview will be telephoned by the research team within four weeks of their four week follow-up appointment at their GP practice (i.e. 4-8 weeks from their initial consultation). This is to ensure that the qualitative data collection does not have an impact on the primary outcome data for the trial, while allowing reasonable recall of the consultation.

Clinicians will be contacted at the end of the recruitment period for the trial to allow them to gain sufficient experience of using the CRP POCT, while minimising the potential impact on practice of carrying out the interviews during the recruitment period.

Analysis

Interviews will be fully transcribed verbatim and checked for accuracy. Data will be analysed using framework analysis. This is a systematic approach to a thematic qualitative analysis that allows for easy comparisons between and within cases, facilitates sharing and discussion of data, and allows for clear linking / access from developed themes to original data (Ritchie & Spencer, 1994). Framework analysis involves five stages: 1.) familiarisation with the data; 2.) development of a thematic framework; 3.) applying thematic codes to all of the data (indexing); 4.) retrieving and summarising coded data in a chart; and 5.) interpreting the data by drawing inferences and pulling together relevant themes. Framework analysis is particularly useful when there are a number of clear research aims that have guided the questions, while allowing new themes to emerge from the data that are relevant to the research question. Dual coding will be carried out for 20% of the interviews to allow for an assessment of coding validity. NVivo qualitative analysis software will be used to assist coding.

14. Trial procedures

14.1 Training of Staff

All staff involved in the trial specific procedures (including recruitment/consent, collection of trial data, application of intervention and clinical assessments) will be trained in the relevant aspects of GCP.

All relevant staff at sites will receive training to ensure they understand the PACE Trial protocol and how to identify potential participants. All staff at each site with delegated responsibilities for any aspect of the PACE study will be provided suitable training to ensure they understand the trial procedure.

Clinicians that will be responsible for making management decisions will be asked to complete a training module that will provide an overview of the aims and rationale for the study, a summary of NICE and GOLD guidance on managing AECOPD, and training in interpreting CRP test results.

Alere will provide practices (who are using an Alere CRP machine) with specific training in using the POCT and conducting the CRP test, including quality control procedures.

Training in taking a sputum sample and throat swab will be provided where required.

All staff taking consent and approaching patients will be trained have clear training and guidelines regarding co-enrolment. In particular they will be told that it should be made clear to participants that they will not be expected to take part in this study if they have participated in any other research within the last 6 months.

14.2 Data collection/assessment

In order to facilitate the process of patient registration and data collection into busy routine clinics, data collection can be conducted by a suitably trained nurse or healthcare assistant instead of or as well as by a general practitioner. Patient follow up will be by telephone calls at one, and two weeks and a face to face visit at four weeks when patients will be assessed and have follow up sampling done. Patients will also be sent a CRQ-SAS through the post to complete and return at six months. The timing and type of assessment is described in table 3.

Table 3. Schedule of assessments

Assessment	**At time of Consent**	**1 week (phone call)**	**2 weeks (phone call)**	**4 weeks (face to face)**	**Patient notes search (NS); post (P))**
Assessment of eligibility	**X**				
Written informed consent	**X**				
Contact details	**X**				
	X				
	X				
Medication history	**X**				
	X				
Temperature	**X**				
Oxygen saturation	**X**				
Antibiotic prescribing	**X**				**X (NS)**
Other prescribed meds for current illness	**X**				
CRP level*	**X**				
CCQ	**X**	**X**	**X**	**X**	
EQ5D	**X**	**X**	**X**	**X**	**X (P)**
Sputum sample **and** throat swab	**X**			**X**	
4 week return visit date	**X**				
Antibiotics use		**X**	**X**	**X**	**X (NS)**
Other meds for AECOPD		**X**	**X**	**X**	
Adverse effects		**X**	**X**	**X**	
Adherence to use of POCT	**X**	**X**	**X**	**X**	
Healthcare contact and use				**X**	**X (NS)**
Mortality**				**X**	**X (NS)**
CRQ-SAS					**X (P)**

*only for patients randomized to the POCT arm

** Deaths during the 4 week follow up period only will be reported as SAEs

14.3 Baseline Assessments

Baseline data and samples should be collected before the participant is randomised. Workflow between the GP and nurse can be adapted based on roles and responsibilities on a practice by practice basis. A contact form will be completed and the best number and time to contact the participant will be recorded. Where possible, a 4 week follow up visit will be booked before the participant leaves the practice.

14.4 Follow-up

The trial team will phone the participants 1 week and 2 weeks post randomisation. Participants will be invited back to the surgery for a face to face visit 4 weeks post randomisation. The CRQ-SAS will also be posted to participants for completion at 6 months. The team will make every effort to adhere to these time-points, but if for any reason it is not possible to phone (or get hold off)/see the participant we will aim to conduct the assessments within the following thresholds:

1 week phone call: -1/+2 working days

2 weeks phone call:-1/+7 working days

4 weeks face to face: -3/+14 working days

6 month notes search: N/A

Phone call – week 1 and 2 The phone calls will be conducted by a member of the trial team or clinical study officer/research nurse working for the local research network. Participants will be given the CCQ and EQ-5D-5L questionnaires at their baseline visit and asked to complete on the appropriate day prior to the telephone interview in order to facilitate completion.

Face to face visit – week 4

The face to face visit appointment will be made at the time of baseline assessments and will be conducted by a member of the clinical team in the GP practice or a clinical study officer/research nurse working for the local research network at the GP practice. Every effort should be made to ensure the participant attends the appointment at, or as close to, 4 weeks from the time of randomisation.

Notes search – Month 6

Data relevant to the study including spirometry results, prescriptions, and health service utilisation will be extracted from the primary care medical records for each participant for the 6 months period following randomisation. In addition, any oral antibiotics prescribed in the 12 months prior to the baseline appointment will be recorded. GP practices will be asked to provide data from a note search or visited by a member of the trial team or clinical study officer/research nurse working for the local research network.

Posted CRQ-SAS and EQ 5D-5L – Month 6

A member of the trial team will post a copy of the CRQ-SAS and EQ-5D-5L to each participant at six months. Participants will be telephoned one week after the due date to remind them to complete over the telephone or to return the questionnaire by post. If the questionnaire is not received by the study team within 1 week of the first telephone reminder, the study team will telephone the participant once more.

Collection of sputum sample and throat swabs

Sputum **and** throat swab samples will be collected at baseline and at the face to face visit at week 4. Participants will be asked to provide a sputum sample and a throat swab. A sample form will be completed and the samples returned in postage paid packaging to

the Public Health Wales Specialist Antimicrobial Chemotherapy Unit (SACU) laboratory, Cardiff. Samples will be kept for potential future analysis, however no human DNA analysis will be done on the sputum or throat swab samples. The sputum and throat swab samples will not be used by the commercial sector. Ethical approval will be sought before any further analyses are carried out.

15. Statistical considerations

15.1 Randomisation

Participants will be randomised in a 1:1 ratio to receive either current best clinical management alone (control) or best clinical assessment with the addition of CRP POCT (intervention). Randomisation will take place remotely using minimisation, with a random element set at 80% to improve the integrity of the randomisation process. The Anthonisen criteria (categorised as type 1, 2 or 3) will be used as a minimisation variable, so that balance is achieved with respect to differing levels of COPD exacerbation severity. Remote allocation will maintain allocation concealment from both the participant and the treating clinician prior to allocation, as this is an unblinded study.

15.2 Sample size

We aim to have sufficient power to detect a 15% reduction from a current estimated antibiotic consumption rate (proportion that take any antibiotics) for AECOPD from 70% to 55% in the four weeks following randomisation. Current estimates suggest that approximately 80% of patients with AECOPD in primary care are prescribed antibiotics (14) and the majority of patients with this illness are likely to initiate their treatment. To show a difference in proportions between 0.70 and 0.55 at the 5% significance level and with 90% power we would need a total of 434 participants, inflating to 544 to account for the loss to follow-up of approximately 20% of participants. We have also aimed to have sufficient power to demonstrate that participants managed with CRP POCT are no worse (non-inferior), compared to those managed without CRP POCT, in terms of their COPD health status two weeks following randomisation. Assuming an expected difference between groups of zero, a non-inferiority margin of 0.3 (lower than the lowest minimal clinically important difference (28) and a common standard deviation of 1.1(29) then based on a one-sided significance level of 0.05 and 90% power we would need 462 participants, inflating to 580 to account for the loss to follow-up of approximately 20% of participants.

Formulating our overall hypothesis using the Intersection-Union test (30), we will carry out our individual sub-hypothesis tests at the 5% level, and if both are significant conclude overall significance at the 5% level. However, power will be affected by the level of correlation between the two outcomes and their respective effect sizes. The impact on overall power is at its greatest when there is zero correlation between outcomes and effect sizes are identical (the overall power is the product of the powers for testing each individual sub-hypothesis) (31, 32), and is increasingly negligible the more correlated outcomes are and the more different effect sizes become. We do not expect our effect sizes to be similar, as our co-primary outcomes are two very different constructs. We also anticipate that the outcomes will not be entirely independent. We

will therefore aim to recruit at least 650 participants to maintain an overall power between 81 and 90%.

Participants will be recruited from approximately 10 practices during the internal pilot, with each practice recruiting an approximate average of 7 participants over 6 months, and 60 practices in the substantive trial, with each practice recruiting an approximate average of 9 participants over 7 months. Our final sample size will provide adequate power to account for the clustering of antibiotic prescribing by practice, assuming an ICC of 0.02.

15.3 Termination of the trial

There is potential for the trial to terminate early if our funder assesses the study as not being feasible following an assessment of progress against our targets at the end of the internal pilot.

16 Adverse Events

16.1 Definitions

Adverse Event (AE): Any untoward medical occurrence in a trial participant which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory finding), symptom, or disease.

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 ***

* Note: The term "life-threatening" in the definition of serious refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

** Note: Hospitalisation is defined as an inpatient admission, regardless of the length of stay, even if the hospitalisation is a precautionary measure, for continued observation. Pre-planned hospitalisation e.g. for pre-existing conditions which have not worsened or elective procedures does not constitute an adverse event.

*** Note: other events that may not result in death are not life-threatening, or do not require hospitalisation may be considered as a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

An SAE occurring to a research participant should be reported to the main REC where in the opinion of the Chief Investigator the event was:

• Related – that is, it resulted from administration of any of the research procedures, and

• Unexpected – that is, the type of event is not listed in the protocol as an expected occurrence

See section 16.4 for the procedure for reporting AEs and SAEs.

16.2 Causality

The assignment of causality should be made by the Investigator responsible for the care of the participant. The Chief Investigator (or Clinical Reviewer Delegate) will also be responsible for making an assessment of causality. In the case of discrepant views on causality between the site and the clinical reviewer, the event will be handled at the highest event categorisation.

Relationship	**Description**
Unrelated	There is no evidence of any causal relationship with the trial/study or intervention
Unlikely	There is little evidence to suggest there is a casual relationship (e.g. the event did not occur within a reasonable time after intervention) with the study/trial or intervention. There is another reasonable explanation for the event (e.g. the participant's clinical condition, other treatment).
Possible	There is some evidence to suggest a causal relationship with the trial/study or intervention (e.g. because the event occurs within a reasonable time after intervention). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a judgement of the causal relationship.

16.3 Expectedness

The assessment of whether or not an SAE is an expected consequence of receiving the intervention will be provided by one of the co-Chief Investigators (or Clinical Reviewer Delegate), it will not be provided by the Investigator responsible for the care of the participant.

In this patient population, acute illness resulting in hospitalisation, new medical problems and deterioration of existing medical problems are expected. PACE POCT is a safe test to undergo and we do not envisage any SAEs resulting from the test itself.

16.4 Reporting procedures

Depending on the nature of the event, the reporting procedures outlined in this protocol should be followed. Any queries concerning serious adverse event reporting should be directed to the trial coordination centre in the first instance.

- Non-serious AEs potentially attributable to antibiotics prescribed for AECOPD will be collected as part of routine follow-up on the week 1, week 2 and week 4 follow-up CRF
- Other 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
- Hospitalisation is expected within this patient population and will be collected and reported as part of routine follow-up (self-reported by patients and recorded on the week 1, week 2 and week 4 follow-up CRFs and by case note review at 6 months) and not subject to expedited reporting on a SAE form
- All other events fulfilling the definition of an SAE , including death, that occur between the time of consent and the 4 week follow-up should be reported to SEWTU by completing and faxing a SAE form to the PACE Trial Manager within 24 hours of the site becoming aware of the event
- Any death occurring after the 4 week follow-up should be reported by telephoning SEWTU (02920 687620) and not subject to expedited reporting on a SAE form
- Any other SAE occurring after the 4 week follow up will not be reported

SEWTU will notify the Sponsor and main REC of all related and unexpected SAEs occurring during the trial within **15** calendar days of the Chief Investigator becoming aware of the event.

All Investigators will be informed of all related SAEs occurring throughout the trial. Local Investigators should report any SAEs as required by their Local Research Committee and/or Research and Development Office.

Contact details for reporting SAEs

Please Fax to:

02920 687612, attention: Janine Bates PACE Trial Manager

Queries:

Tel: 02920 687517 (Mon to Fri 09.00 – 17.00)

16.5 Urgent Safety Measures (USMs)

An urgent safety measure is an immediate change in a trial procedure or temporary halt to a trial procedure, put in place prior to authorisation by the main REC and Sponsor in order to protect participants from any immediate hazard to health and safety following new safety information (SAE or other information received from an external source). The Sponsor, Chief Investigator or Principal Investigator may carry out USMs to protect participants from immediate harm. Any urgent safety measure relating to this trial should be notified to the Sponsor and ethics committee within three days of the action being taken in the form of a substantial amendment.

17 Analysis

17.1 Primary Analysis

Our two co-primary outcomes will each be evaluated using the intention-to-treat principle, and then combined using the criteria specified in Table 4 below.

For the COPD health status outcome, we will also conduct a Complier Average Causal Effect (CACE) analysis in order to produce a conservative analysis that adjusts for intervention receipt whilst preserving a comparison of groups as randomised.

Specific secondary and subgroup analyses are also planned.

There will be no planned interim analysis. The assessment made for the internal pilot will be based on recruitment and follow-up rates with no analysis of outcomes.

All results will be presented as estimates of treatment effects, with associated confidence intervals and p-values.

TABLE 4

Criteria for judging the intervention to be successful/ unsuccessful		
	Patient-reported COPD health status worse in the CRP group	**Patient-reported COPD health status not worse in the CRP group**
Antibiotic consumption no different	Intervention unsuccessful	Intervention unsuccessful
Antibiotic consumption different (lower in the CRP group)	Intervention unsuccessful	Intervention successful

Primary analyses: Our first primary analysis will compare the odds of consuming an antibiotic during the four weeks following randomisation, in each trial arm, using logistic regression. Our second primary analysis will compare the mean CCQ score between each trial arm using linear regression, with a one-sided 95% confidence interval constructed to assess non-inferiority. We will test if a two level model is required due to clustering by practice and fit a single level model if it is not needed. Modelling assumptions will be tested, with appropriate adjustments made in the presence of any violations. Missing primary outcome data is likely to be minimal, but will be accounted for in the intention to treat analysis by fitting generalised linear mixed models, which assume that data are missing at random given observed measurements.

Our second primary analysis, testing the non-inferiority of CRP versus no CRP with respect to the CCQ, will be based on our pre-specified margin of 0.3. However, should

our observed difference be between 0.3 and 0.4 (0.4 is the minimal clinically important difference (MCID) for the outcome), we will consider our results more fully, reflecting on differences found in antibiotic prescribing and secondary outcomes (e.g. antibiotic resistance, EQ-5D etc.) in the two trial arms. In other words, we are using a conservative margin for our non-inferiority test, but if the difference is larger than this conservative margin but still smaller than the MCID then we will consider the result in light of the potential gain for individuals and society.

17.1.1 Sub-group & interim analysis

Differential intervention effects on the primary outcomes will be assessed by fitting interaction terms in the primary models between trial arm and the following:

- COPD severity (Gold I/II/III)
- Severity of COPD exacerbation (Anthonisen criteria type 1/2/3)

Two exploratory mediation analyses will be conducted using causal modelling techniques to determine whether the effect of the intervention on; i) Antibiotic prescribing and ii) COPD health status is mediated through steroid prescribing.

17.2 Secondary Analysis

Differences between trial arms in COPD health status over the first four weeks will be estimated by fitting a mixed model to the CCQ scores at 1, 2 and 4 weeks, with responses nested within participants and baseline controlled for as a covariate. Differences between trial arms in most recent FEV1 (one of the clinical history items recorded at baseline) will be assessed by fitting an analysis of covariance (ANCOVA) model with FEV1 as a covariate. A comparison will be made between arms of the use of antibiotics for any reason (not just AECOPD-related) in the four weeks following randomisation, other COPD medication in the four weeks following randomisation, and antibiotic prescribing at the index consultation. The two arms will be compared using logistic regression. Differences in the proportion of participants experiencing adverse effects from medication prescribed will also be assessed by fitting a logistic regression model. The proportion of participants hospitalised will be compared between trial arms by fitting a logistic regression model. The subset of hospitalisations that are due to pneumonia will be separately compared. Similarly, proportion of participants consulting in primary / secondary care will be compared between trial arms by fitting a logistic regression model. The mean CRQ-SAS at six months will be compared between trial arms using linear regression.

17.3 Microbiological Analysis

A sputum sample and a throat swab will both be obtained at baseline and at week 4. Sputum sample appearance will be noted then each sample will be processed using routine microbiological procedures. Any potential pathogenic bacteria (*S. pneumoniae*, *H. influenzae/parainfluenzae*, *Pseudomonas* species, *Enterobactericeae*

and S. aureus) will be identified using the Matrix Assisted Laser Desorption Ionising Time of Flight Mass Spectrometry (MALDI-ToF-MS and semi-quantitative counts recorded. Throat swabs will be put into broth solution and spiral plated onto non selective (Blood agar, chocolate agar) and selective agar containing antimicrobials (cephalosporin, penicillin, tetracycline, levofloxacin & erythromycin). Both potential pathogen and commensal bacteria (alpha-haemolytic streptococci) will be identified by MALDI-ToF-MS and colony counts recorded. Susceptibilities will be performed on all sputum and throat swab bacteria by disc diffusion using European Committee on Antimicrobial Susceptibility Testing (EUCAST) methodology and breakpoints. The presence of any pathogen plus the total bacterial load from sputa and throat swab cultures will be recorded; proportional quantification of resistant isolates will be determined from the selective media. All pathogens recovered, sputum samples and remaining broth from throat swabs will be stored at -80°C.

17.4 Economic Evaluation

The primary aim of CRP POCT is to reduce inappropriate antibiotic prescribing conditional on no negative health effect as measured by the CCQ. Accordingly, a cost effectiveness analysis assessing total health service costs against one of the primary outcomes (% patients consuming an antibiotic within the next four weeks) will be undertaken from a health service perspective. Direct costs will include all resources used in training GPs/nurses and purchase/running costs of CRP equipment. Indirect costs will include prescribed antibiotics, repeat consultations and all other health service resource use. Patient borne costs, including absences from work, will be collected but reported separately. Results will be reported in the form on an Incremental Cost Effectiveness Ratio (ICER), showing the additional cost of producing an extra unit reduction in antibiotic prescribing. This can be compared with other interventions whose aim is to reduce inappropriate antibiotic prescribing. If the main trial fails to demonstrate non-inferiority in terms of the CCQ then the intervention will be regarded as non-cost effective.

A second economic analysis will be undertaken in the form of a within-trial cost utility analysis (CUA), also from a health service perspective, assessing total costs against health related quality of life measured using EQ-5D-5L which allows generation of Quality Adjusted Life Years (QALY). No conditions for non-inferiority in health outcomes will be imposed. Failure to demonstrate non-inferiority in terms of CCQ suggests that the CUA result is likely to lie to the left of the y axis of the cost effectiveness plane, implying either that the intervention is dominated (NW quadrant = not cost effective) or that it would only be cost effective if the extra saving per QALY sacrificed is above a wiliness-to-accept threshold (SW quadrant). The effects of reduced antibiotic prescribing on antimicrobial resistance, however, are not being assessed within this study. Given the predicted huge costs of further increases in antimicrobial resistance (33), the intervention may still be considered to be worthwhile from an economic perspective even if it does not meeting conventional cost effectiveness decision rules. Using bootstrap methods, 95% confidence intervals around differences in mean costs between groups will be estimated. Results will be reported as ICERs showing the extra cost of producing one extra QALY or the extra savings achieved by sacrificing one additional QALY. Probabilistic sensitivity analyses will be undertaken to show the probability of the ICER falling below a range of willingness to pay (accept) thresholds, including the current UK NICE willingness to pay threshold of

£20,000 to £30,000 per QALY. Given the short follow up period, discounting will not be applied.

17.5 Process Evaluation

We will explore the effect of the intervention in those who received the intervention as intended using instrumental variable/causal modelling methods. For reasons given for over-riding the antibiotic prescribing guidance in the CRP POCT group (recorded as free text by clinicians at initial consultation), content analysis will be used to develop a coding framework to allow categorisation of responses. Qualitative data will be audio-recorded, transcribed verbatim and analysed using inductive thematic analysis, facilitated by qualitative analysis software (NVivo). This will allow for the identification of salient themes emerging from the data (rather than being restricted by pre-defined themes) relating to: the way that the intervention was implemented in practice; the acceptability of the intervention to patients and clinicians, and; contextual issues that may have impacted on treatment fidelity and effectiveness. A sample of the transcripts (20%) will be coded by a second researcher and inter-rated reliability of coding will be assessed.

18 Data storage & retention

Electronic data will be stored on fire-walled University computers, and only accessible to researchers involved in the study. All procedures for data storage, processing and management will be in compliance with the Data Protection Act 1998. All paper records will be stored in a locked filing cabinet, with keys available only to the trial management team. The trial statistician will carry out analysis. All essential documents generated by the trial will be kept in the trial master file.

All data will be kept for 15 years in line with Cardiff University's Research Governance Framework Regulations for clinical research. This data will be stored confidentially on password protected servers maintained on the Cardiff University Network.

19 Trial closure

The end of the trial will be considered as the last date of data capture.

20 Regulatory issues

The Co-Chief Investigators shall be responsible for ensuring that the clinical study is performed in accordance with the following:

- Declaration of Helsinki (Seoul, 2008;).
- ICH Harmonised Tripartite Guideline for Good Clinical Practice.
- Research Governance Framework for Health and Social Care (Welsh Assembly Government 2nd Edition, September 2009 and Department of Health 2nd Edition, July 2005)

The storage, analysis, and disposal of clinical samples will accord with the requirements of the Human Tissue Act (2004). Data transfer across participant organisations will be closely monitored. A Privacy Risk Assessment in each regional centre (Cardiff, London and Oxford) will proactively identify and ameliorate risks of breaches to confidentiality and clearly designate the named individuals who will be allowed to access identifiable information. Published outcomes of the trial will not enable identification of the individual participants.

20.1 Ethical and research governance approval

This study protocol will be submitted to a Research Ethics Committee (REC) recognised by the United Kingdom Ethics Committee Authority (UKECA) for review and approval. A favourable ethical opinion must be obtained from the REC before commencement of any trial procedures (including recruitment of patients) occurs.

All substantial protocol amendments must be approved by the REC responsible for the study, in addition to approval by NHS R&D. Minor amendments will not require prior approval by the REC.

If the study is stopped due to adverse events it will not be recommenced without reference to the REC responsible for the study.

The outcome of the study (e.g. completed) will be reported to the REC responsible for the study within 90 days of completion of the last patient's final study procedures. In the event of the study being prematurely terminated a report will be submitted to the REC responsible for the study within 15 days.

A summary of the Trial Report will be submitted to the REC responsible for the study within one year of completion of the last subject's final study procedures.

20.2 Risks and anticipated benefits for trial participants and society, including how benefits justify risks

Biomarker guided antibiotic prescribing has been evaluated in the hospital setting and was found to be safe (34). CRP POCT testing is widely used around the world, especially in Scandinavian countries where it is commonly used to help guide antibiotic prescribing decisions for AECOPD in the community. It has been evaluated as a tool to guide antibiotic prescribing for LRTI in the community and found to be safe. This study is based on the latest evidence from our placebo-controlled trial of antibiotics for AECOPD, in which we measured CRP in all patients. These results, confirmed by our observational study in TROMSO, provide clear evidence that patients with a low CRP are unlikely to be harmed by withholding antibiotics. However, we have taken a conservative approach in developing our algorithm, and have recommended that clinicians base their prescribing decision on the most useful clinical features in addition to the CRP level.

Participants in the intervention arm will receive targeted treatment, which means not only avoiding antibiotic prescribing for those who are unlikely to benefit, but also identifying those with high test values who are more likely to benefit from antibiotic prescribing. Unnecessary antibiotic prescribing results in unnecessary adverse effects and increases the risk of becoming colonised (or infected) by resistant bacteria. The potential benefits for society include a greater understanding of the management of AECOPD, leading to improved outcomes and better targeting of antibiotic treatment to those most likely to benefit, which may help contain antibiotic resistance - a major threat to public health.

The main potential risk for participants is that not being prescribed antibiotics will lead to adverse clinical outcomes. We estimate that the risk of this is low. Furthermore, COPD health status is one of our co-primary outcomes and we will carefully monitor a range of potential adverse effects. All Suspected Unexpected Serious Adverse Reactions (SUSARs) will be reported in line with GCP guidance and we will establish an IDMC to provide ongoing monitoring of outcomes. Participants and their primary care clinicians will be informed that participants have the right to seek alternative treatments, and/or withdraw from the study at any time without having to give a reason. Recruitment will cease if the TSC, considers that a clearly superior method of management or significant unexpected risks have been identified. The highest degree of compliance with good research

governance (see below) will ensure patient confidentiality. All potentially eligible patients will be informed of the study by letter from their GP when they are well (not-exacerbating). This will ensure that patients with COPD are aware of the study and are not presented with too much new information when they attend their GP Practice with an exacerbation and are feeling unwell and uncomfortable. This letter will provide information about the study including the potential risks and benefits of taking part. Eligible participants will be identified at the time of consulting, and at this time possible risks and benefits and known risks will be conveyed face-to-face and any concerns raised and discussed.

20.3 Consent

All participants will be fully informed about the trial through the Participant Information Sheet (PIS), supplemented by verbal explanations from the practice nurses or GPs. Randomisation (chance of receiving one of the trial arms) will be explained in understandable terms in the PIS, which will be further clarified by the trained clinician. The PIS will also include details of any potential effects of not receiving an antibiotic along with the risks and benefits of the trial. All participants will be asked to provide written, informed consent before the trial commences. They will be given as much time as they require to ask questions and decide whether or not they would like to take part in the trial.

20.4 Confidentiality

The Chief Investigators and PACE Study team will preserve the confidentiality of participants in accordance with the Data Protection Act 1998. All data will be handled according to the principles of the Data Protection Act, especially for sensitive, personal data. Data will be anonymised and stored on a password protected computer located in secure University buildings and appropriately backed up. Any data transfer will be closely monitored. A privacy risk assessment will proactively identify and ameliorate risks of breaches of confidentiality and clearly designate the named individuals who will be allowed to access identifiable information. All data will be retained for up to 15 years post study closure in line with Cardiff University's procedures.

20.5 Indemnity

Cardiff University will provide indemnity and compensation in the event of a claim by, or on behalf of participants, for negligent harm as a result of the study design and/or in respect of the protocol authors/research team. Cardiff University does not provide compensation for non-negligent harm.

20.6 Trial sponsorship

Cardiff University will act as sponsor for trial. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

An Memorandum of Understanding will be developed between the Sponsor, Chief Investigator and SEWTU where all delegation of responsibilities will be listed.

20.7 Funding

This trial is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (HTA ref: 12/33/12).

20.8 Audits & inspections

The trial is participant to inspection by the NIHR as the funding organisation. The study may also be participant to inspection and audit by Cardiff University under their remit as sponsor.

21 Trial management

PACE will be led by Co-Chief Investigators (CIs) based at Cardiff University and Oxford University, Chris Butler and Nick Francis, who together with co-investigators from London, will ensure the optimal integration of the three centres. PACE will be conducted in collaboration between a trials unit (South East Wales Trials Unit - SEWTU) and regional recruitment centres in London and Oxford. SEWTU will provide overall study coordination, including data management, design of data collection and entry tools, monitoring data quality, and liaison with the research laboratory, and will manage recruitment in Wales. All three recruitment centres have strong patient recruitment potential and track records backed up by international excellence in research methods and are supported by national schools of primary care research (Wales School of Primary Care Research, Department of Primary Care and Public Health Sciences-King's College London in England) and research networks (NISCHR- CRC, PCRN-GL, Thames Valley PCRN).

21.1 TMG (Trial Management Group)

The TMG will consist of the Chief Investigators, co-applicants and collaborators, trial manager, trial statistician and trial administrator. The role of the TMG is to help set up the trial by providing specialist advice, input in and comment on the trial procedures and documents (patient information sheets, protocol, etc.) and advise on the promotion and the running of the trial. The group will meet monthly during the trial. This group will also review and advise on the reporting of serious adverse events (SAEs). The meetings will be predominantly via audio conference, but with an initial face-to-face meeting and then face-to-face meetings at least every six months. This mix of face-to-face and frequent audio conferences has been highly successful on other collaborations between these teams. Additional meetings will be held on specific topics during the set-up phase covering data management and training.

21.2 Internal Project Group

This group will consist of the Chief Investigators, trial manager, trial statistician and trial administrator and will meet weekly to discuss the day-to-day issues that arise from the trial.

22 Data monitoring & quality assurance

A risk assessment has determined the study as Low Risk Non-Investigational Medicinal Products (IMP) Study, which has determined the level of monitoring required through adhering to SEWTUs risk assessment standard operating procedure (SOP) and monitoring SOP. Monitoring will be performed according to ICH GCP and the trial monitoring plan. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the

monitors will verify that the trial is conducted and data are generated, documented and reported in compliance with the protocol and GCP

22.1 TSC (Trial Steering Committee)

A TSC will meet at least annually, consisting of an independent chair, and two/three other independent members. We will ensure that a patient representative and all appropriate disciplines are covered in choosing the TSC members. The first meeting will be before the trial commences to review the protocol and arrange the timelines for the subsequent meetings. If necessary, additional/more frequent meetings may occur. The Chief Investigators, trial manager and statistician will attend as observers. The TSC will provide overall supervision for the trial and provide advice through its independent chair. The ultimate decision for the continuation of the trial lies with the TSC. The TSC will have oversight of the interactions with Alere to ensure that independence of the research team is maintained. Members will be required to sign up to the remit and conditions as set out in the TSC Charter

22.2 IDMC (Independent Data Monitoring Committee)

An IDMC will be established and will meet at least annually. The Committee will consist of an independent chair and two/three other independent members. Again, we will ensure that all appropriate disciplines are covered in choosing the IDMC members. The first meeting will take place before the trial commences in order to review the protocol and agree on timelines for future meetings. The main role of the IDMC is to review the data periodically and makes recommendations to the TSC.

Members will be required to sign up to the remit and conditions as set out in the IDMC Charter.

23 Publication policy

All publications and presentations relating to the trial will be authorised by the Trial Management Group and will follow the SEWTU publication policy. In addition to the required final report and monograph for the HTA Programme, we will publish the main trial results in international peer-reviewed journals and present at national and international scientific meetings. With the assistance of our collaborators and patient representatives, we will disseminate the trial findings to a wide NHS and general audience. If the CRP POCT test is found to be effective in this context, the clinical algorithm and associated training will be made available online. The trial protocol will be published. Articles will be prepared reporting the main effectiveness findings, cost-effectiveness and process evaluation for international peer-reviewed journals. We will produce an annual newsletter in two formats; one aimed at health professionals, academics, and policy makers, and the other for the general public and patients. Press releases will be generated at key points, including at project initiation and when the results have been peer reviewed and made publically available. Relevant and accessible summaries of findings and presentations will be aimed at key stakeholder groups such as Primary Care Trusts and General Practices, Royal Colleges, Medical Schools, and relevant patient groups (including Breathe Easy, the British Lung Foundation, COPD Exchange, and Age UK). We will feed results into a range of antibiotic stewardship programs including the RCGP ASPIC online program

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25 Appendices

1. Pilot phase patient Interview topic guide

Introduction

- This informal interview is part of the PACE research study, which you have been taking part in over the last month or so.
- I'd like to ask you some questions about your experience of having an acute exacerbation, or 'flare up' of your COPD and about what it has been like to take part in this project.
- We'd really like to hear about your experience so that we can improve the way that we run the project in future.
- This interview will be audio-recorded. The recording will be treated with the strictest confidentiality and may be listened to by the research team but by no-one else. Your GP will not have access to this recording. The recording will not be labelled with your name, and any written record or report derived from it will be fully anonymised.
- Do you have any questions you would like to ask?

1. Before the consultation

People with COPD sometimes have a 'flare up', or an 'exacerbation' of their condition, when they have a sudden worsening of their symptoms. About a month ago, you contacted your GP because you were having a flare up of your chest condition, and you decided that you would like take part in the PACE research project.

- To get us started, could you tell me a bit about your recent flare up of your COPD (which led you to visit your doctor and take part in this study)?
  [Prompts: What it was like? When did it start? What do you think caused it?]

- Did you take anything for your symptoms before you saw the doctor?
  [Prompts: If so, what did you take?]

- Would you have normally gone to your GP for this flare up (that is, if you weren't taking part in this research study)?
  [Prompts: Why/Why not?]

2. The consultation

- When you saw the doctor, did they do any examinations or tests?
  [Prompts: What sort? How did these go?]

- What did the doctor suggest to improve your symptoms?
  [Prompts: What advice were you given? Were you given any medication?]

- Did your doctor prescribe antibiotics?

  [Prompts: Did you think you needed antibiotics? Have you been prescribed antibiotics before for these kinds of symptoms? Did you ask for antibiotics? Or,

did your doctor suggest antibiotics? Did you feel involved in the decision? If you were prescribed antibiotics, did you finish the course?]

- Did you go back to see your GP again about this flare up of your COPD?

  [Prompt: If yes, why?]

- How did you feel about the consultation you had with your GP about this flare up of your COPD?
  [Prompts: Were you satisfied? Did you feel reassured? Did you feel you got the right information? Did you feel you got the right treatment?]

3. The CRP point of care test

Pilot phase interviews: Intervention group only

- Were you offered a finger prick blood test during your consultation with your GP?

- What did you think about having the finger prick blood test?

  [Prompts: How did you feel about having the blood sample taken from your finger? Were there any problems / delays? Did you think it was useful? Did you have any concerns?]

- People have different views about what the finger prick blood test is for. In your opinion, what was it testing for?

- How would you feel about doctors using this test more often to help them decide when antibiotics should be prescribed for COPD flare ups? This would mean coming in to the surgery to see your doctor before starting antibiotics that you may already have at home.

4. Research Processes

As part of the PACE research study, you have been asked for a range of information about yourself and your chest condition, as well as being asked to give some samples.

- Could you tell me what it has been like for you to take part in this research study?

  [Prompts: Were there any problems? What were the best things about taking part? What were the worst things about taking part?]

Please ask about the following topics only if not mentioned above:

- Did you feel that you were given the right information about the PACE research project before you took part?

  [Prompts: Was the information clear? Did you have all the information you needed? Did we miss out anything important? Was there anything that might put people off taking part? Was it helpful for you to receive information early on, before you had a flare up?]

- Do you recall being asked to not start any rescue medication before seeing your GP or nurse? If so, what did you think about that?

  [Prompts: Was this OK? Did you have any concerns?]
- In this research study, you would have been randomly selected to either have your usual care from your GP, or to have an additional finger-prick blood test. How did you feel about that?

[Prompts: Did you have a preference for which group you wanted to be in? Did you feel the process was fair? How did you feel about being in the usual care/blood test group?]

- You were asked to give a sputum sample. How did you feel about that?

  [Prompts: Was it OK? Did you have any problems with giving a sample?]

- Did your nurse or doctor take a throat swab?

  [If yes, prompts: How was this? Did you have any problems giving a sample?]

- One of our research team should have tried to telephone you one week and two weeks after you visited your GP to ask you some questions. Did this happen?

  [Prompts: If yes, how did this go? Were the questions OK? Was the length of the phone call OK? Did you have any concerns about this?]

- We also asked you to come back to your GP's surgery after 4 weeks for some
- follow-up tests. Were you able to do this?

[Prompts: If yes, how did you feel about it? Was it convenient? Were the tests OK?]

- Is there anything we could change to make it easier for people to take part in this study?

5. General

So far, we have been talking about your recent flare up of your chest condition. I'd like to ask you a few more general questions about how flare ups of COPD are managed at your GP's surgery.

- How do you feel about the treatment you receive for your COPD when you have a 'flare up'?
  [Prompts: Would you change anything about the support you get? What are the best things about how it is managed? What are the worst things?]

- In your opinion, when should antibiotics be prescribed for 'flare ups' of COPD?

  [Prompts: Should they always be used for flare ups, or only in some situations? Why?]

- In your view, what are the pros and cons of taking antibiotics for 'flare ups' of COPD?

- How do you think doctors usually decide whether to prescribe antibiotics for 'flare ups' of COPD?

- Do you have any further comments?

Thank you very much for taking part in this interview.

2. Pilot phase clinician Interview topic guide

Introduction:

- I would like to ask you about your experiences of using the C-reactive protein (CRP) point of care test with patients who have symptoms of an acute

exacerbations of COPD *(if this is applicable to you)* and to ask you what it has been like to take part in the PACE research study.

- This interview will be audio-recorded. The recording will be treated with the strictest confidentiality and may be listened to by the research team but by no-one else. The recording will not be labelled with your name and any written record or report derived from it will be fully anonymised.
- Are there any questions you would like to ask me before we start?
- *[Complete written or verbal consent as applicable. For verbal consent, confirm that the consent process will be audio-recorded].*
-

1. Using the CRP POCT

In the PACE study, we asked primary care practices to use a CRP point of care test with patients who have symptoms of an acute exacerbations of COPD who had been randomly allocated to the relevant group.

- To get us started, could you talk me through how the CRP point-of care test was used in your practice?

  [Prompts: Who carried out the test? At what point was the test carried out, e.g. during the consultation/before the consultation. How did you integrate it into your consultations? Can you describe/give an example of a consultation where the CRP point-of care test was used?]

- ***If not stated above:*** Did you use the CRP point of care tests with any patients yourself?
  - If **yes**, proceed to next question.
  - If **no**, skip to section 4 (Research processes)

- Were you able to use the CRP point-of care test with every patient who had been randomised to the intervention trial arm?

  [Prompts: If not, why? Were there problems with the testing equipment? Did you have concerns? Did any patients decline?]

- Did use of the CRP point-of-care test make a difference to the way you managed acute exacerbation of their COPD?

  [Prompt: Did you discuss the test result with patients? How did consultations using the CRP POCT compare with your usual consultations? To what extent did it influence your treatment decisions?]

- Do you feel that using the CRP point-of-care test have an influence on whether you prescribed antibiotics for AECOPD?

  [Prompt: How important was the CRP point-of-care test result relative to other aspects of your assessment of your patients?]

- How do you think your patients felt about the CRP point-of-care test?

  [Prompts: Do you think patients found it reassuring? Was it helpful in discussing antibiotics with them? Did it have an effect on the dynamics of the consultation?]

- What was your overall opinion of the CRP point-of-care test used in this study?

  [Prompts: Was it useful? How did you feel about using it? What were the advantages? What were the disadvantages? Did you have any concerns about use

of the test? Has it changed the way you view AECOPD? Has it changed the way you manage AECOPD?]

- Would you want to use this test in your routine management of acute exacerbations of COPD?

  [Prompts: Why/Why not? Would you use it with all patients or just in specific situations?]

We'd like to find out more about what it is like to use the specific CRP point-of-care test equipment we used in the PACE study (Afinion CRP).

1. What was the CRP test like to use?

   [Prompts: Were there problems with any aspect of the testing equipment? Was it easy or difficult to use?]

2. The CRP point-of-care test required getting a finger-prick blood sample from patients. How did this go?

   [Prompts: Were there problems with any aspect of the finger prick procedure?]

3. How did you find interpreting the CRP test results?

   [Prompts: Did you experience any technical problems? Was it easy or difficult to interpret?]

2. Training

- What did you think of the training provided in use and interpretation of the CRP point-of-care test?

  [Prompts: What training did you use? Was it useful? Did you have enough information? Is there any other information you would have liked? How much time did it take to complete? Was this OK? Is there anything you would change about the training?]

3. Research Process

- We're interested in your experience of taking part in this research. Could you tell me what it has been like for you to take part in the PACE study?

  [Prompts: Were there any problems? What were the best things about taking part? What were the worst things about taking part? Did you have any specific concerns about: completing the baseline CRFs; collection or processing of samples; follow up assessments in the practice at 4 weeks]

- We have tried to keep the process of identifying and recruiting a patient as simple as possible, partly by allowing the tasks to be split by different members of the practice team. Can you talk us through the process you used in your practice?

  [Prompts: Could you give us your opinion on how you think it went? Who did what, and how was this decided? How did it work for you? Did you have to change the way you did it part way through the study? Can you think of ways that it could have been improved? Were there any steps or processes that you think could be dropped?]

Please ask about the following topics only if not mentioned above:

- We asked your practice to identify potentially eligible patients at the beginning of the winter season and to send them information about the study by post. How did this go?

  [Prompts: Was this easy or hard to do? Did you think this was useful?]

- Were you involved in taking consent and randomisation?

  [Prompts: If so, how did these processes go? If not, who took consent and randomised patients in your practice? Were there any problems? What could have been done better? Were there eligible patients that you didn't randomise? If so, why?]

- Patients were asked to contact their GP when they next had an exacerbation of their COPD. How do you think this worked in practice?

  [Prompts: Was it possible to provide patients with appointments at short notice? Do you think this affected whether people wanted to/were able to take part?]

- COPD patients were asked not to start antibiotics, or 'rescue medication', before being seen by their GP if they wanted to take part in the PACE study. What did you think about this?

  [Prompts: Did you have any concerns? Do you think this might have put patients off taking part?]

- Is there anything else you think we need to consider before rolling this study out to more practices?

4. General

So far, we've been talking specifically about the PACE study. I'd like to ask you a few more general questions about your views on managing acute exacerbations of COPD and point of care tests in guiding antibiotic prescribing.

- What are the main challenges with managing acute exacerbations of COPD in primary care?

- **[For prescribing clinicians only]**: How do you usually decide whether you will prescribe antibiotics in the management of acute exacerbations of COPD?

  [Prompts: How easy or difficult is it to judge whether antibiotics should be prescribed? What factors do you generally use to guide your antibiotic treatment decisions?]

- Do you think there is a role for point-of-care tests in guiding antibiotic prescribing decisions more generally in primary care (i.e. for conditions other than acute exacerbations of COPD)?

  [Prompts: What are the advantages/disadvantages? Are they needed? Do they have an effect on consultations with patients? Are there other ways of guiding decisions about antibiotic prescribing that should be explored?]

- Do you have any other comments?
-

PACE Patient Interview Topic Guide: Main Trial Phase

Introduction

- This is an informal interview and part of the PACE research study, which you have been taking part in over the last month or so.
- I'd like to ask you some questions about your experiences of having an acute exacerbation, or 'flare up' of your COPD and what it has been like to take part in this study.
- This interview will be audio-recorded. The recording will be kept strictly confidential and may be listened to by the research team but by no one else. Your GP will not have access to this recording. The recording will not be labelled with your name, and any written record or report derived from it will be fully anonymised.
- Are there any questions you would like to ask me before we start?

Before the consultation

People with COPD often have a 'flare up', or an 'exacerbation' of their condition, where they experience a worsening of their symptoms.

1. Could you tell me a bit about your recent flare up of your COPD (which led you to visit your doctor and ended up with you agreeing to take part in this study)?
[Prompts: What was it like? How did you know you were having a flare up? Do you get different types of flare ups? How long had it been going on for when you decided to go to your surgery? What made you decide to go to the surgery? Do you find it difficult deciding when to go? Why is that? Do you have any particular rules or triggers that make you feel that now is the time to see someone? What do you think caused your flare up? Do you think your flare ups get caused by different things?]

2. Did you do anything for your symptoms before you saw the doctor?
[Prompts: If so, what did you do and when/how do you decide ? Talk me through what you do when you feel that your flare up is getting worse. Did you decide to increase the amount of the medicines you were taking (including your inhalers) or start taking new medicines when your chest started getting worse? Were these part of a 'rescue pack' that your GP has prescribed for you? If so, how did you decide to start taking your rescue pack? Did you take any over the counter medicines? Did you try any homeopathic or other alternative therapies?]

3. Would you have normally gone to your GP for a flare up like this (that is, if you weren't taking part in this research study)?

4. Did you have any problems getting an appointment?
[Prompts: Why/Why not?]

The consultation

5. When you saw the doctor, did he/she do any examinations or tests in the surgery?
[Prompts: What sort? How did these go? Do you have any views on what tests should be done when you go to the GP with a flare up like this? Were you offered a finger prick blood test during your consultation with your GP?]

6. What did you think about having the finger prick blood test?
[Prompts: How did you feel about having the blood sample taken from your finger? Were there any problems / delays? Did you think the test was useful? Did

you have any concerns? Did the doctor/or nurse seem to find the test easy to do? Did it take much time? Did you feel confident about having the test? Did you feel that the test was safe?]

7. People have different views about what the finger prick blood test is for. What do you think the test was for?

8. What did the doctor suggest to improve your symptoms?
[Prompts: Did the doctor tell you what they thought had caused the flare up? What advice were you given? Were you given any medication?]

9. Did your doctor prescribe antibiotics?
[Prompts: Did you think you needed antibiotics? Have you been prescribed antibiotics before for these kinds of flare-ups? Did you ask for antibiotics? Or, did your doctor suggest antibiotics? Did you feel involved in the decision? How did you feel about being prescribed (or not being prescribed) antibiotics? If you were prescribed antibiotics, did you finish the course? Why/why not?. Do you usually take antibiotics you are given for a flare up as prescribed?]

10. How did you feel about the consultation you had with your GP about this flare up of your COPD?
[Prompts: Did you feel involved with the decisions about your treatment? Were you satisfied? Did you feel reassured? Did you feel you got the right information? Did you feel you got the right treatment? How did you feel about the decision to use (or not use) antibiotics? Is there anything that you would have liked to be different?]

11. Did you go back to see your GP again about this flare up of your COPD?
[Prompt: If yes, why? Do you think that having to go back had anything to do with the first consultation you had (when you entered the study)? Where you given a finger-prick blood test when you went back?]

General

So far, we have been talking about your recent flare up of your COPD. I'd like to ask you a few more general questions about how your flare ups of COPD are managed at your GP's surgery.

12. How do you feel about the treatment you receive for your COPD when you have a 'flare up'?
[Prompts: Do you find it easy to see your doctor? Would you change anything about the support you get? What are the best things about how it is managed? What are the worst things?]

13. Have you ever been admitted to the hospital with a flare-up of your symptom, or do you regularly see any other specialists for your COPD?
[Prompts: if yes, when, how many times and did this impact on how you manage your symptoms?}

14. In terms of healthcare services for COPD, what do you think would be the most important thing to improve?

15. In your opinion, when should antibiotics be prescribed for 'flare ups' of COPD?
[Prompts: Should they always be used for flare ups, or only in some situations? Why?]
16. In your view, what are the benefits of taking antibiotics for 'flare ups' of COPD?

[Prompts: Do you think it reduces the length of exacerbations? Do you think it prevents you from developing something more serious?]

17. And in your opinion, are there any drawbacks of taking antibiotics for 'flare ups' of COPD?

18. Have you ever had problems taking antibiotics? Have you ever had to take several different courses to get rid of infections?
[Prompts: if yes, what problems, when? How serious was it? Does this impact on how you manage your symptoms?]

19. How would you feel about being given antibiotics to keep at home that you can take if you have a flare up? Doctors sometimes call this a 'rescue pack'.
[Prompts: What are the benefits? What are the drawbacks? Would you prefer to see a doctor before taking antibiotics that you have at home?]

20. Do you think anything else, including any of your other medications like inhalers and steroids, are more helpful than antibiotics for flare-ups?

21. What do you know about antibiotic resistance?
[Prompts: What do you think antibiotic resistance means? Do you think it is your body, or the bacteria that become resistant to antibiotics? What do you think causes bacteria to become resistant? Do you think that there are any particular problems with using antibiotics too often for people with COPD? Can antibiotics be used when you have a virus?]

22. How do you think doctors usually decide whether to prescribe antibiotics for 'flare ups' of COPD?
[Prompts: Do you think they take into account what patients want? Do you think there are any particular symptoms they take into account?]

23. How would you feel about doctors using this finger prick test more often to help them decide when antibiotics should be prescribed for COPD flare ups? This would mean coming in to the surgery to see your doctor before starting antibiotics that you may already have at home in your rescue pack.
[Prompt: Would you mind waiting longer at the surgery in order to have a test and get the result?]

24. What do you think about the idea of having antibiotics and steroids at home that you can take when you have a flare up? Sometimes doctors call this a 'rescue pack'.
[Prompt: Do you know the differences between antibiotics and steroids and when each should be used? Have you received any training or information on using rescue packs?]

Research Process

As part of the PACE research study, you have been asked for a range of information about yourself and your chest condition, as well as being asked to give some samples.

25. Could you tell me what it has been like for you to take part in this research study?
[Prompts: Were there any problems? What were the best things about taking part? What were the worst things about taking part? Would you recommend taking part to someone else?]

26. Do you have any other comments?

Thank you very much for taking part in this interview.

4. PACE Clinician Interview Topic Guide: Main Trial

Introduction

- I would like to ask you about your experiences of using the C-reactive protein (CRP) point of care test with patients who have symptoms of an acute exacerbations of COPD (if this is applicable to you) and to ask you what it has been like to take part in the PACE research study.
- This interview will be audio-recorded. The recording will be treated with the strictest confidentiality and may be listened to by the research team but by no-one else. The recording will not be labelled with your name and any written record or report derived from it will be fully anonymised.
- Are there any questions you would like to ask me before we start?
- [Complete written or verbal consent as applicable. For verbal consent, confirm that the consent process will be audio-recorded].
-

Using the CRP POCT

In the PACE study, we asked primary care practices to use a CRP point of care test with patients who have symptoms of an acute exacerbations of COPD who had been randomly allocated to the relevant group.

1. To get us started, could you talk me through how the CRP point-of care test was used in your practice?

[Prompts: Who carried out the test? At what point was the test carried out, e.g. during the consultation/before the consultation. How did you integrate it into your consultations? Can you describe/give an example of a consultation where the CRP point-of care test was used?

2. Have there been any cases where the CRP test result was surprising based on the patient's clinical symptoms? (If yes, how did this affect your prescribing decision?)

3. If not stated above: Did you use the CRP point of care tests with any patients yourself?

- If yes, proceed to next question.
- If no, skip to section 4 (Research processes)

5. Were you able to use the CRP point-of care test with every patient who had been randomised to the intervention trial arm?

   [Prompts: If not, why? Were there problems with the testing equipment? Did you have concerns? Did any patients decline?]

6. Did the use of the CRP point-of-care test make a difference to the way you managed acute exacerbations of COPD?

[Prompt: Did you discuss the test result with patients? How did the consultation using the CRP POCT compare with your usual consultations? To what extent did it influence your treatment decisions?]

7. Do you feel that using the CRP point-of-care test had an influence on whether you prescribed antibiotics for AECOPD?

   [Prompt: How important was the CRP point-of-care test result relative to other aspects of your assessment of your patients?]

8. How do you think your patients felt about the CRP point-of-care test?

   [Prompts: Do you think patients found it reassuring? Was it helpful in discussing antibiotics with them? Did it have an effect on the dynamics of the consultation?]

9. What was your overall opinion of the CRP point-of-care test used in this study?

   [Prompts: Was it useful? How did you feel about using it? What were the advantages? What were the disadvantages? Did you have any concerns about use of the test? Has it changed the way you view AECOPD? Has it changed the way you manage AECOPD?]

10. Would you want to use this test in your routine management of acute exacerbations of COPD?

    [Prompts: Why/Why not? Would you use it with all patients or just in specific situations?]

    We'd like to find out more about what it is like to use the specific CRP point-of-care test equipment we used in the PACE study (Afinion CRP).

11. What was the CRP machine like to use?

    [Prompts: Were there problems with any aspect of machine? Was it easy or difficult to use

12. What were the CRP cartridges like to use?

    [Prompts: Were there problems with any aspect of using the cartridges? Were they easy or difficult to use?]

13. The CRP point-of-care test required getting a finger-prick blood sample from patients. How did this go?
    [Prompts: Were there problems with any aspect of the finger prick procedure?]

14. How did you find interpreting the CRP test results?

    [Prompts: Did you experience any technical problems? Was it easy or difficult to interpret? Was the CRP algorithm easy to interpret and use?]

15. Have there been any cases where the CRP test result was surprising based on the patient's clinical symptoms? (If yes, how did this affect your prescribing decision?)

16. Did you use the CRP test controls to calibrate the machine?

    [Prompts: How often, and how did you find this?]

17. Did you find it easy to store the CRP cartridges and controls in your surgery?

Training

18. What did you think of the training provided in use and interpretation of the CRP point-of-care test?

    [Prompts: What training did you use? Was it useful? Did you have enough information? Is there any other information you would have liked? How much time did it take to complete? Was this OK? Is there anything you would change about the training?]

Research Process

19. We're interested in your experience of taking part in this study. Could you tell me what it has been like to take part in the PACE study overall?

    [Prompts: Were there any problems? What were the best things about taking part? What were the worst things about taking part?]

20. How do you think your patients felt about taking part?

General

So far, we've been talking specifically about the PACE study. I'd like to ask you a few more general questions about your views on managing acute exacerbations of COPD, and using point of care tests to guide antibiotic prescribing.

21. What do you think are the main challenges with managing acute exacerbations of COPD in primary care?

22. [For prescribing clinicians only]: How do you usually decide whether you will prescribe antibiotics in the management of acute exacerbations of COPD?

    [Prompts: How easy or difficult is it to judge whether antibiotics should be prescribed? What factors do you generally use to guide your antibiotic treatment decisions?]

23. What is your approach to discussing decisions about antibiotic prescribing with patients?

[Prompts: Do you think patients expect antibiotics? How do you go about involving patients in this decision? How do patients respond to your suggestions? What are the main challenges of discussing this with patients? What information is most important to get across to patients about your antibiotic prescribing decisions?]

24. What advice do you generally give COPD patients regarding using rescue packs?

    [Prompts: Do all COPD patients have rescue packs in your surgery? What are the advantages of having rescue packs at home? What would be the disadvantages of having rescue packs at home? Do you discuss with patients how they have been using their rescue packs?]

25. Do you think there is a role for point-of-care tests in guiding antibiotic prescribing decisions more generally in primary care (i.e. for conditions other than acute exacerbations of COPD)?

    [Prompts: What are the advantages/disadvantages? Are they needed? Do they have an effect on consultations with patients? Are there other ways of guiding decisions about antibiotic prescribing that should be explored?]

26. In terms of healthcare services for COPD, what do you think would be the most important thing to improve?

27. Do you have any other comments?

Thank you very much for taking part in this interview.