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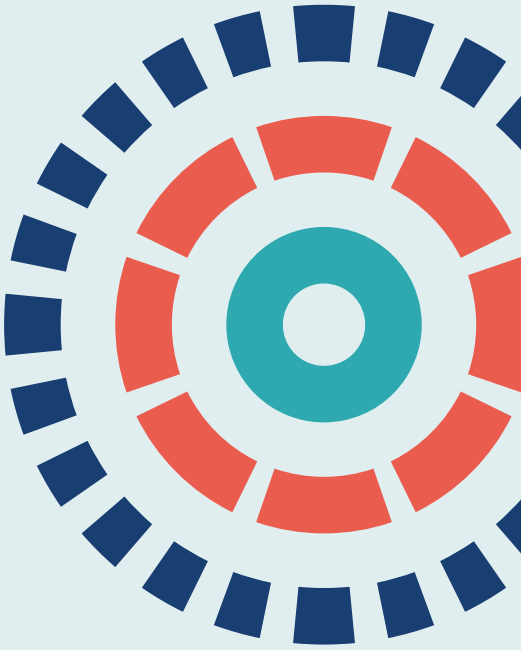

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C-reactive protein point-of-care testing for safely reducing antibiotics for acute exacerbations of chronic obstructive pulmonary disease: the PACE RCT

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This report

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Abstract

C-reactive protein point-of-care testing for safely reducing antibiotics for acute exacerbations of chronic obstructive pulmonary disease: the PACE RCT

Nick A Francis,[1]* David Gillespie,[2] Patrick White,[3] Janine Bates,[2] Rachel Lowe,[2] Bernadette Sewell,[4] Rhiannon Phillips,[1] Helen Stanton,[2] Nigel Kirby,[2] Mandy Wootton,[5] Emma Thomas-Jones,[2] Kerenza Hood,[2] Carl Llor,[6] Jochen Cals,[7] Hasse Melbye,[8] Gurudutt Naik,[9] Micaela Gal,[10] Deborah Fitzsimmons,[4] Mohammed Fasihul Alam,[11] Evgenia Riga,[12] Ann Cochrane[3] and Christopher C Butler[13]

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Background: Most patients presenting with acute exacerbations of chronic obstructive pulmonary disease (AECOPD) in primary care are prescribed antibiotics, but these may not be beneficial, and they can cause side effects and increase the risk of subsequent resistant infections. Point-of-care tests (POCTs) could safely reduce inappropriate antibiotic prescribing and antimicrobial resistance.

Objective: To determine whether or not the use of a C-reactive protein (CRP) POCT to guide prescribing decisions for AECOPD reduces antibiotic consumption without having a negative impact on chronic obstructive pulmonary disease (COPD) health status and is cost-effective.

Design: A multicentre, parallel-arm, randomised controlled open trial with an embedded process, and a health economic evaluation.

Setting: General practices in Wales and England. A UK NHS perspective was used for the economic analysis.

Participants: Adults (aged ≥ 40 years) with a primary care diagnosis of COPD, presenting with an AECOPD (with at least one of increased dyspnoea, increased sputum volume and increased sputum purulence) of between 24 hours' and 21 days' duration.

Intervention: CRP POCTs to guide antibiotic prescribing decisions for AECOPD, compared with usual care (no CRP POCT), using remote online randomisation.

Main outcome measures: Patient-reported antibiotic consumption for AECOPD within 4 weeks post randomisation and COPD health status as measured with the Clinical COPD Questionnaire (CCQ) at 2 weeks. For the economic evaluation, patient-reported resource use and the EuroQol-5 Dimensions were included.

Results: In total, 653 participants were randomised from 86 general practices. Three withdrew consent and one was randomised in error, leaving 324 participants in the usual-care arm and 325 participants in the CRP POCT arm. Antibiotics were consumed for AECOPD by 212 out of 274 participants (77.4%) and 150 out of 263 participants (57.0%) in the usual-care and CRP POCT arm, respectively [adjusted odds ratio 0.31, 95% confidence interval (CI) 0.20 to 0.47]. The CCQ analysis comprised 282 and 281 participants in the usual-care and CRP POCT arms, respectively, and the adjusted mean CCQ score difference at 2 weeks was 0.19 points (two-sided 90% CI –0.33 to –0.05 points). The upper limit of the CI did not contain the prespecified non-inferiority margin of 0.3. The total cost from a NHS perspective at 4 weeks was £17.59 per patient higher in the CRP POCT arm (95% CI –£34.80 to £69.98; $p = 0.408$). The mean incremental cost-effectiveness ratios were £222 per 1% reduction in antibiotic consumption compared with usual care at 4 weeks and £15,251 per quality-adjusted life-year gained at 6 months with no significant changes in sensitivity analyses. Patients and clinicians were generally supportive of including CRP POCT in the assessment of AECOPD.

Conclusions: A CRP POCT diagnostic strategy achieved meaningful reductions in patient-reported antibiotic consumption without impairing COPD health status or increasing costs. There were no associated harms and both patients and clinicians valued the diagnostic strategy.

Future work: Implementation studies that also build on our qualitative findings could help determine the effect of this intervention over the longer term.

Trial registration: Current Controlled Trials ISRCTN24346473.

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Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/hta24150).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

A&E	accident and emergency
AE	adverse event
AECOPD	acute exacerbation of chronic obstructive pulmonary disease
AMD	adjusted mean difference
AOR	adjusted odds ratio
CACE	complier average causal effect
CCQ	Clinical COPD Questionnaire
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRF	case report form
CRN	Clinical Research Network
CRP	C-reactive protein
CRQ-SAS	Chronic Respiratory Disease Questionnaire Self-Administered Standardized
CSRI	Client Service Receipt Inventory
CUA	cost–utility analysis
EQ-5D	EuroQol 5-Dimensions
EQ-5D-3L	EuroQol 5-Dimensions, three-level version
EQ-5D-5L	EuroQol 5-Dimensions, five-level version
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	general practitioner
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
IQR	interquartile range
ITT	intention to treat
LRTI	lower respiratory tract infection
MITT	modified intention to treat
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PACE	Primary care use of A C-reactive protein point of care test to help target antibiotic prescribing to patients with acute Exacerbations of chronic obstructive pulmonary disease who are most likely to benefit
POCT	point-of-care test
PPI	patient and public involvement
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life-year
RCT	randomised controlled trial
REC	Research Ethics Committee
SAE	serious adverse event
SD	standard deviation
SE	standard error

Plain English summary

People with chronic obstructive pulmonary disease (COPD) often experience flare-ups known as acute exacerbations of chronic obstructive pulmonary disease. Antibiotics are prescribed for most flare-ups, but they do not always benefit patients and may cause harm, such as side effects or subsequent infections that are resistant.

Rapid point-of-care tests (POCTs) can be used to help determine when antibiotics are more likely to be needed. C-reactive protein (CRP) is a marker of inflammation that can be measured with a POCT. Patients with flare-ups and a low CRP value are less likely to benefit from antibiotics. The PACE trial asked whether or not measuring CRP with a POCT could lead to fewer antibiotics being consumed for flare-ups, without having negative effects for patients.

We aimed to recruit 650 patients with a COPD flare-up from primary care. Patients were randomly assigned to either (1) usual care with the addition of a CRP POCT, or (2) usual care without the addition of the test. Antibiotic use over the first 4 weeks and patients' self-assessment of their health 2 weeks after enrolment were measured in both groups.

Patients in the CRP test group used fewer antibiotics than those managed as usual, and had improved patient-reported outcomes. Costs were a little higher in the CRP POCT group. Interviews with patients and clinicians found that they appreciated the CRP test being included in the decision-making process.

Scientific summary

Background

Unnecessary antibiotic use drives antimicrobial resistance, wastes resources, may cause adverse effects and may distract from potentially more effective interventions for individuals. Point-of-care tests (POCTs) for acute infections are being promoted by government, by industry and in clinical guidelines to reduce inappropriate antibiotic prescribing, help contain antimicrobial resistance and improve patient outcomes. However, most evaluations of POCTs have examined analytic performance only, and there have been few trials evaluating clinical effectiveness and cost-effectiveness in the context in which POCTs are intended to be used. About 4.5% of the population over the age of 45 years live with diagnosed chronic obstructive pulmonary disease (COPD), and about half of these people experience one or more acute exacerbations of chronic obstructive pulmonary disease (AECOPD) that require medical treatment each year. Over 2 million antibiotic courses are prescribed for AECOPD each year in the UK, and most of these are issued in primary care. Although some patients with AECOPD are helped by these prescriptions, many are not, and so some antibiotics may simply damage the microbiome. Among patients admitted to hospital, a bacterial aetiology was identified in 30%, a viral agent was identified in 23%, both bacterial and viral agents were identified in a further 25%, and 20% of the AECOPDs were caused by other factors. The antibiotic prescribing recommendations for primary care management of AECOPD are generally based on clinical features alone (Anthonisen criteria, namely increased breathlessness, increased sputum volume and increased sputum purulence) (Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987;**106**:196–204). These features are subjective and have insufficient diagnostic accuracy to predict which patients can safely be managed without antibiotics.

C-reactive protein (CRP) is an acute phase protein that rises rapidly in infections and can be measured easily at the point of care, and it is considered the most selective biomarker to confirm AECOPD. A randomised controlled trial in primary care found no difference in clinical cure between patients with AECOPD treated with antibiotics and those treated with placebo who had a CRP level of < 40 mg/l. The availability of CRP POCT results may, therefore, help guide prescribing decisions for AECOPD to reduce antibiotic consumption, reduce antimicrobial resistance and improve patient outcomes. However, the clinical effectiveness and cost-effectiveness of CRP POCT have not yet been evaluated in a pragmatic controlled trial in primary care.

Objective

We aimed to establish whether or not the addition of a CRP POCT to usual care for AECOPD in primary care safely and cost-effectively reduces antibiotic consumption for AECOPD.

Methods

Trial design

The PACE (Primary care use of A C-reactive protein point-of-care test to help target antibiotic prescribing to patients with acute Exacerbations of chronic obstructive pulmonary disease who are most likely to benefit) trial was a multicentre, parallel-arm, individually randomised controlled open trial with embedded health economics and qualitative process evaluations, conducted between September 2015 and February 2017 in UK general medical practices.

Intervention guidance

All participating sites were provided with information on the current best practice for managing AECOPD, which included a brief summary of National Institute for Health and Care Excellence and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidance, and were provided with a desktop CRP POCT Afinion device [Alere Afinion™ AS100 Analyzer, Alere Inc. (now Abbott Diagnostics), IL, USA]. Clinicians were given training in the use of the POCT and guidance on interpreting the test results, which emphasised that the decision about antibiotic prescribing should be based on a comprehensive assessment of the likely risks and benefits, given the patient's underlying health status and clinical features. In addition, the guidance indicated that for patients with a CRP level of < 20 mg/l, antibiotics are unlikely to be beneficial and usually should not be prescribed; for patients with a CRP level of 20–40 mg/l, antibiotics may be beneficial, mainly if purulent sputum is present; and for patients with a CRP level of > 40 mg/l, antibiotics are likely to be beneficial.

Eligibility, recruitment and randomisation

Men or women were eligible if they were aged ≥ 40 years, had a primary care diagnosis of COPD, presented with an AECOPD (with at least one of increased dyspnoea, increased sputum volume and increased sputum purulence) of between 24 hours' and 21 days' duration, and provided informed, written consent.

Participants were allocated to the trial arms using remote online computerised randomisation.

Data collection

Baseline data collected included the number of days the patient had AECOPD symptoms, the patient's medical history and clinicians' examination findings.

A sputum sample, when obtainable, and throat swab samples were taken, and participants self-completed the Clinical COPD Questionnaire (CCQ) and the EuroQol 5-Dimensions (EQ-5D) questionnaire prior to randomisation. Clinicians recorded their antibiotic prescribing and other management decisions for all participants after randomisation and assessment.

Participants were followed up with telephone calls at week 1 and week 2, and a face-to-face consultation at 4 weeks post randomisation, during which a further throat swab and sputum sample (when available) were taken. At 6 months, the Chronic Respiratory Disease Questionnaire Self-Administered Standardized (CRQ-SAS) and EQ-5D questionnaires were posted to participants, who completed these and returned them using provided stamped addressed envelopes, and we collected relevant data from electronic medical records.

Clinicians were asked to carry out a CRP POCT as part of their assessment of participants allocated to the intervention (CRP POCT arm). For patients allocated to usual care (control arm), clinicians were asked not to use CRP POCT in their management of those patients' AECOPD at any time during participation.

Outcome measures

We used two co-primary outcomes because any reduction in antibiotic consumption would have to be considered alongside any negative impact on patient recovery. The first co-primary outcome was patient-reported antibiotic consumption for AECOPD within 4 weeks post randomisation. The second co-primary outcome was COPD health status (total score) measured with the CCQ at 2 weeks post randomisation.

Sample size

The study aimed to have sufficient power to detect a 15% reduction from an estimated 70% of patients consuming antibiotics for AECOPD during the 4 weeks following randomisation, and sufficient power to demonstrate that participants managed with the CRP POCT do no worse (non-inferior) than those managed without the CRP POCT, in terms of their COPD health status measured with the CCQ 2 weeks post randomisation. Assuming an expected difference between the arms of zero, a non-inferiority margin of 0.3 [smaller than the lowest minimal clinically important difference and a common standard deviation (SD) of 1.1], based on a one-sided significance level of 0.05 and 90% power, the study needed 462 participants, inflated to 580 to account for the loss to follow-up of approximately 20% of participants. It was also anticipated that the outcomes would not be entirely independent. Therefore, we aimed to recruit at least 650 participants to maintain an overall power between 81% and 90%.

Clinical effectiveness and cost-effectiveness analyses

The main clinical effectiveness analysis was based on a modified intention-to-treat population, which included all randomised participants who provided outcome data, regardless of protocol deviations or intervention received. All planned analyses were described in detail in a statistical analysis plan.

A within-trial health economic analysis was undertaken from a UK NHS perspective that assessed CRP POCT implementation costs in primary care and subsequent health-care costs within the trial follow-up period of 6 months. A cost-effectiveness analysis based on the co-primary outcome of antibiotic consumption at 4 weeks and a cost–utility analysis at 6 months were performed. Furthermore, a cost–consequences analysis and a budget impact analysis were conducted and the robustness of the results was tested in sensitivity analyses.

Process evaluation

A qualitative process evaluation was undertaken to facilitate the interpretation of results and assist with implementation planning. Semistructured telephone interviews were carried out with 20 purposively sampled patients and 20 primary care staff. A topic guide focused on experiences of the management of AECOPD, the acceptability, implementation and potential mechanisms of the CRP POCT intervention and contextual factors that could influence future implementation. Audio-recordings were transcribed verbatim and analysed using framework analysis.

Results

Baseline characteristics

In total, 653 participants were randomised from 86 general practices between January 2015 and February 2017. Three withdrew consent and one was randomised in error (the patient had been randomised, but the clinician then noted that this patient was ineligible and so their baseline data were destroyed), leaving 324 usual-care and 325 CRP POCT participants. The mean age was 68.1 (SD 9.42) years; 51.6% of participants were men; 10.8% of participants had mild COPD (GOLD I), 54.8% of participants had moderate COPD (GOLD II), 28.1% of participants had severe COPD (GOLD III) and 6.3% of participants had very severe COPD (GOLD IV); the mean ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) was 0.6 (SD 0.13); the mean percentage predicted FEV_1 was 59.8% (SD 20.04%); the mean number of days with symptoms prior to consultation was 6.9 (SD 5.13) days; the mean baseline CCQ total score was 3.3 (SD 1.14) points; and the baseline health utility (EQ-5D) was 0.7 (SD 0.25). Overall, no pathogens were detected in 95 out of 386 baseline sputum samples (24.6%), bacterial pathogens were only detected in 79 out of 386 (20.5%), viral/atypical pathogens were only detected in 123 out of 386 cases (31.9%) and both bacterial and viral/atypical pathogens were detected in 89 out of 386 cases (23.1%). Participants in both trial arms were well matched for these and other characteristics at baseline.

Primary outcome

In total, 537 out of the 649 randomised participants contributed to the primary analysis of self-reported antibiotic consumption at 4 weeks post randomisation (82.7%), and 563 contributed to the primary analysis of CCQ total score at 2 weeks post randomisation (86.7%). Antibiotics were *consumed* for AECOPD by 212 (77.4%) usual-care participants and 150 (57.0%) CRP POCT participants [adjusted odds ratio (AOR) 0.31, 95% confidence interval (CI) 0.20 to 0.47]. The adjusted mean CCQ score difference at 2 weeks was –0.19 (two-sided 90% CI –0.33 to –0.05) points. The upper limit of the CI did not contain the prespecified non-inferiority margin of 0.3.

Antibiotic prescribing at index consultation and 4-week follow-up

Antibiotic prescribing at the index consultation was ascertained for all but one participant, and 22% fewer participants in the CRP POCT arm were *prescribed* antibiotics (47.7% in the usual-care arm vs. 69.7% in the CRP POCT arm, AOR 0.31, 95% CI 0.21 to 0.45), and 21% fewer participants were prescribed antibiotics over the 4-week follow-up (59.1% vs. 79.7%, AOR 0.30, 95% CI 0.20 to 0.46).

Antibiotic prescribing and C-reactive protein values at index consultation

A total of 97.5% (317/325) of participants allocated to the CRP POCT arm reported receiving a CRP POCT during the recruitment consultation, and the median CRP value was 6 mg/l (interquartile range 5–18.5 mg/l); 76.0% of participants (241/317) had CRP levels of < 20 mg/l. Antibiotics were prescribed for 33% of those patients with a CRP level of < 20 mg/l in the CRP POCT arm at the index consultation.

Secondary outcomes

There was no evidence of a difference between the arms regarding symptoms sometimes attributed as adverse effects from antibiotics and other COPD treatments (AOR 0.79, 95% CI 0.44 to 1.39; $p = 0.410$), primary or secondary care consultations during the 6 months following randomisation (AOR 1.39, 95% CI 0.46 to 4.15; $p = 0.559$), or pneumonia diagnoses at 4 weeks (AOR 1.57, 95% CI 0.28 to 8.84; $p = 0.608$) and 6 months (AOR 0.73, 95% CI 0.29 to 1.82; $p = 0.495$). There was no evidence to conclude that there were any differences between the arms for CRQ-SAS outcomes at 6 months.

No meaningful or statistically significant differences were found between the arms at 1 month in the potential pathogens and antibiotic resistant isolates from sputum, or in resistance in commensal and potentially pathogenic organisms isolated from throat swabs.

Adverse events

Two participants, both in the usual-care arm, died during the first 4 weeks following randomisation: these serious adverse events were not related to the intervention or to trial participation.

Economic evaluation

Reduced antibiotic costs at the initial consultation were offset by higher total medication costs over the following 6 months, mainly caused by a 5.4% increase in prescribing of inhaled medication in the CRP POCT arm. COPD-related primary care contacts were lower in the intervention arm, with 2.7% fewer general practitioner visits. Although outpatient attendances were reduced in the CRP POCT arm (4.1% fewer appointments at 4 weeks and 6.7% fewer at 6 months), the secondary care cost for any condition was higher for all follow-up periods as a result of increased inpatient length of stay for a small number of intervention patients. The total incremental cost was £17.59 at 4 weeks and £126.26 at 6 months, driven mainly by the higher inpatient cost and the cost of CRP testing. If only COPD-related health-care costs are considered, the cost in both arms was similar, with the CRP test cost of £11.31 per test slightly offset by savings in health-care resource use. The mean incremental cost-effectiveness ratios were £222 (95% CI –£42.00 to £518.14) per 1% reduction in antibiotic consumption compared with usual care at 4 weeks and £15,251 (95% CI £2959 to £22,813) per quality-adjusted life-year gained at 6 months. Patients in the CRP POCT arm had fewer days off work, with reduced costs of productivity loss of £510.42 (95% CI –£989.56 to –£31.28; $p = 0.022$) per patient reporting periods of worktime missed.

Process evaluation

Patients participating in the qualitative evaluation felt that the CRP POCT was useful in detecting infection and targeting treatment more appropriately, and that it seemed quick and easy to use. Clinicians reported enhanced confidence in making management decisions and reduced decisional ambiguity when withholding antibiotics, and felt that the CRP POCT was a useful tool for communicating with and reassuring patients. They were keen to emphasise that the test should be used alongside, and not as a replacement for, clinical assessment. Cartridge preparation time and the cost of the equipment presented a significant barrier when implementing the test.

Conclusions

A CRP POCT diagnostic strategy resulted in a 20% absolute reduction in patient-reported antibiotic *consumption* over 4 weeks and in clinician antibiotic *prescribing* at the index consultation, and no clinically important change in patient-reported condition-specific quality of life, without evidence of an increase in total COPD-related costs. The use of the CRP POCT strategy was broadly acceptable to patients and clinicians. There were no associated harms identified in the trial, although clinicians indicated that the time and costs associated with the CRP POCT needed careful consideration.

Awareness of receiving the POCT may have contributed to enhanced COPD health status; however, this real-world effect needed to be captured. As awareness of intervention allocation may have an impact on participant help-seeking, and, as capturing this is critical to assessments of cost-effectiveness, this was an open trial.

C-reactive protein POCT strategies in primary care have been shown to safely and cost-effectively reduce antibiotic prescribing for acute cough; however, only a small minority of participants in those studies had AECOPD, and none reported effects on antibiotic consumption rather than antibiotic prescribing.

We confirmed that bacterial infection is a likely trigger for AECOPD in a minority of patients, and that there may be potential for further safe reductions in antibiotic use for AECOPD, given that one-third of participants with a CRP level of < 20 mg/l were nevertheless prescribed antibiotics.

This trial provides good evidence that CRP POCT testing (with the associated guidance for clinicians that was used in this trial) to guide antibiotic prescribing decisions for AECOPD in primary care is safe and effective. Further research, building on our qualitative findings, could help guide effective implementation.

Trial registration

This trial is registered as ISRCTN24346473.

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Chapter 1 Introduction

Background

Point-of-care tests (POCTs) for acute infections are being promoted by government, by industry and in clinical guidelines to reduce inappropriate antibiotic prescribing, help contain antimicrobial resistance and improve patient-reported outcomes.[1–4] Whereas POCTs are frequently subjected to evaluations of analytic performance, diagnostic strategies are often introduced into routine care before their clinical effectiveness has been determined in rigorous clinical trials and without an understanding of their cost-effectiveness using relevant health and service delivery outcomes.

Antibiotic use

Better targeting of antibiotics in acute exacerbations of chronic obstructive pulmonary disease (AECOPDs) represents a major opportunity for antimicrobial stewardship and improved patient care. Over 80% of all antibiotics are prescribed in the community,[5] with high prescribing of broad-spectrum antibiotics a particular concern. AECOPD accounts for over 2 million antibiotic prescriptions each year in the UK.[6] Half of patients with chronic obstructive pulmonary disease (COPD) experience one or more exacerbations needing medical treatment each year.[7,8] Over 70% of patients presenting with AECOPD in primary care are prescribed an antibiotic, accounting for 4.6% of all primary care antibiotic prescriptions every year.[9] COPD patients are an important group who are at risk of significant mortality, morbidity and hospitalisation and, as such, are more likely to be prescribed broad-spectrum antibiotics.[10] However, many AECOPD are triggered by non-bacterial causes, such as viral infections and environmental factors including common pollutants and weather. It has been estimated that approximately 70% of AECOPDs are triggered by an infection and 30% are caused by environmental factors. Of the 70% that are triggered by an infection, potential pathogenic bacteria are isolated in 20–58% of clinical samples, while pathogenic respiratory viruses can be detected in approximately 50%.[11–13] Among COPD patients hospitalised as a result of an exacerbation, the causal infectious agents were identified as 29.7% bacterial, 23.4% viral and 25% viral/bacterial.[14]

The overuse of antibiotics drives antimicrobial resistance[15] and is facilitated by the unnecessary consumption of antibiotics for COPD. Antimicrobial treatment in patients with COPD decreases the infecting load but does not usually entirely eradicate organisms in the airways, increasing the risk of resistant bacteria in COPD patients.[16] Infections of antibiotic-resistant *Streptococcus pneumoniae* in patients with COPD are associated with antibiotic exposure.[17,18] A meta-analysis[5] of seven studies of respiratory tract bacteria that comprised 2605 participants showed that the pooled odds ratio for resistance was 2.4 [95% confidence interval (CI) 1.4 to 3.9] and 2.4 (95% CI 1.3 to 4.5) within 2 and 12 months of antibiotic treatment, respectively. The unnecessary use of antibiotics for AECOPD not only contributes to the increasingly pressing public health threat of antibiotic resistance, but also poses a risk to the individual, as it may increase the risk of subsequent antibiotic-resistant exacerbations and hasten disease progression. The indiscriminate use of antibiotics in patients with COPD is particularly high risk because the respiratory tracts of those affected are frequently colonised with potential pathogens.[19] Using unnecessary antibiotics also increases the risk of patient side effects, wastes money and undermines self-care.[20]

Current antibiotic prescribing recommendations for general practitioners (GPs) are generally based on symptoms alone.[21] In 1987, Anthonisen *et al.*[22] defined three types of exacerbation based on the presence of one, two or three of the following features: increased dyspnoea, increased sputum production and increased sputum purulence. Exacerbations with all three of these features were defined as type 1 exacerbations, those with two of these features were defined as type 2 exacerbations, and those with only one feature,

in combination with an upper respiratory tract infection within the previous 5 days, a fever without another cause, increased wheezing, increased cough or a > 20% increase in respiratory rate or heart rate compared with baseline, were called type 3 exacerbations. Anthonisen *et al.*[22] demonstrated an association between these exacerbation types and benefit from antibiotics, and these features became widely adopted as a guide to when to prescribe antibiotics. However, the features are subjective and are insufficiently diagnostically accurate to enable clinicians to predict patients who can safely be managed without antibiotics. A Cochrane systematic review[23] of the use of antibiotics for managing exacerbations of COPD comprised 16 trials (*n* = 2068 participants) and reported that there was insufficient evidence of effectiveness to guide antibiotic prescribing decisions in primary care. Our placebo controlled trial of antibiotics for AECOPD in primary care indicated that benefit from antibiotics for AECOPD was limited largely to those who had a raised C-reactive protein (CRP) level (CRP level refers to CRP concentration measured in serum).[24] More effective strategies are required to ensure that antibiotics are used most effectively for managing AECOPD, so that antibiotic treatment can be targeted at those most likely to benefit and effective non-antibiotic treatment can be targeted at those who are unlikely to benefit from antibiotics.

C-reactive protein

C-reactive protein is an acute-phase protein found in blood. The serum level of CRP increases rapidly during infections, particularly in severe bacterial infections. A prospective evaluation of 36 biomarkers[25] found that CRP level was the most selective biomarker to confirm an AECOPD and, in combination with Anthonisen criteria, produced an area under the curve of 0.88 (95% CI 0.82 to 0.93), indicating that the biomarker had good diagnostic accuracy. High levels of serum CRP is correlated with sputum purulence and raised serum leucocyte counts, and the serum level of CRP is higher in the presence of bacterial infection.[24,26] CRP levels rise in patients with AECOPD and is correlated with the number of Anthonisen criteria present and the degree of airflow limitation in hospitalised patients.[27,28] As CRP levels are more likely to be raised when there is bacterial infection, the treatment effect of antibiotics increases with higher values of CRP.[29]

In our previous study[30] examining predictors of treatment with antibiotics and systemic corticosteroids for acute exacerbations of asthma and COPD, we found that > 50% of COPD patients experiencing an AECOPD had a CRP level of < 8 mg/l, and that chest examination findings, a raised CRP value and decreased oxygen saturation were stronger predictors of prescribing antibiotics and systemic corticosteroids than respiratory symptoms. We found marginal benefit from antibiotic treatment in patients with AECOPD who had only one or two Anthonisen criteria, and using Anthonisen criteria to predict benefit from antibiotic treatment produced an area under the curve of 0.708 (95% CI 0.616 to 0.801). Adding CRP increased this to an area under the curve of 0.842 (95% CI 0.760 to 0.924).[31] Based on these data, we anticipated that using a CRP test alongside clinical assessment might make it possible to safely reduce the antibiotic prescription rate for this condition to around 45%.

C-reactive protein POCTs are widely available and are already commonly used to help guide antibiotic prescribing decisions, including for lower respiratory tract infections (LRTIs) and AECOPD in primary care in a number of European countries (mostly Scandinavian).[32] In two trials[33,34] evaluating the use of a CRP POCT to help target antibiotic treatment for LRTIs in primary care, antibiotics were prescribed to 53% and 48% of patients in each trial's usual-care group, respectively, and to 31% and 33% of patients managed by clinicians using a CRP POCT (with training). However, only small numbers had COPD (< 10% in one study[33] and < 20% with asthma or COPD in the other[34]). CRP POCT was cost-effective in reducing antibiotic prescribing for LRTIs when there was no or low willingness to pay for the tests.[35,36] Now that better and more rapid CRP POCTs are available,[37] there is potential for this technology to be widely used for a variety of acute infections in primary care to better guide antibiotic prescribing and, in doing so, to help reduce unnecessary antibiotic consumption and thus contain antibiotic resistance.

The PACE randomised controlled trial: overall aim

The clinical effectiveness and cost-effectiveness of using a CRP POCT in addition to usual clinical assessment to guide antibiotic prescribing for AECOPD has not been evaluated in a well-powered, pragmatic, individually randomised controlled trial (RCT) in primary care. The PACE (Primary care use of A C-reactive protein point of care test to help target antibiotic prescribing to patients with acute Exacerbations of chronic obstructive pulmonary disease who are most likely to benefit) trial, therefore, aimed to determine whether or not using a CRP POCT in addition to usual care to guide prescribing decisions for AECOPD reduces antibiotic consumption without having a negative impact on COPD health status.

Chapter 2 Clinical effectiveness methods

Summary of trial design

The PACE trial was a multicentre, parallel-arm, open, individually randomised (1 : 1) controlled trial of the clinical effectiveness and cost-effectiveness of CRP POCT in addition to usual care to guide antibiotic treatment decisions for AECOPD on safely reducing patient antibiotic consumption. The study involved general practices that were part of primary care research networks in the UK. Participants presenting with AECOPD to participating practices were randomised to clinical management based on usual care alone (control arm) or to usual care with the addition of a CRP POCT (intervention arm) to guide antibiotic prescribing. This was an open, pragmatic trial with no blinding of participants or clinicians, as we aimed to assess the effects of the intervention in comparison with current usual practice.

Clinical effectiveness objectives

Primary objective

The primary objective was to determine whether or not the addition of a CRP POCT (with training on test use and advice on interpretation) to usual care for managing AECOPD leads to a reduction in antibiotic consumption for AECOPD without having a negative impact on COPD health status, compared with usual care alone.

Secondary objectives

The secondary objectives were to assess the effect of using a CRP POCT for AECOPD in primary care on:

- all-cause antibiotic consumption during the first 4 weeks
- antibiotic prescribing at the index consultation
- use of other COPD treatments, including oral steroids, during the first 4 weeks
- primary and secondary care consultations [including out of hours, accident and emergency (A&E) visits and hospitalisations] during the subsequent 6 months
- incidence of pneumonia during the first 4 weeks and from the 4-week follow-up to 6 months
- adverse effects from antibiotics and other medication prescribed for AECOPD during the first 4 weeks
- COPD health status, as measured using the Clinical COPD Questionnaire (CCQ), at weeks 1, 2 and 4
- health utility, as measured using the EuroQol 5-Dimensions (EQ-5D) at 1, 2 and 4 weeks and at 6 months
- disease-specific health-related quality of life (HRQoL) and Chronic Respiratory Disease Questionnaire Self-Administered Standardized (CRQ-SAS) at 6 months
- prevalence of potentially pathogenic bacteria cultured from sputum at 4 weeks and the proportion of bacteria that are resistant
- prevalence of commensal organisms cultured from throat swabs at 4 weeks and the proportion of bacteria that are resistant.

Changes made to the objectives are outlined in *Appendix 1*, *Table 30*.

The objectives of the qualitative process evaluation and the health economic evaluation are outlined in *Chapters 4* and *5*, respectively.

Internal pilot

An internal pilot study was carried out in 15 general practices in Wales from January 2015 to August 2015. The aim of the pilot study was to assess the recruitment potential, adherence to the intervention allocation and the proportion of participants in whom both primary outcomes could be measured. The prespecified criteria for the success of the internal pilot were at least 1.5 participants recruited per open site per month (excluding the first 2 months), 80% of participants reporting receiving a finger-prick blood test concordant with their allocated intervention arm, and 80% of recruited participants for whom we could ascertain both components of the co-primary outcome. The pilot phase met these criteria, enabling progression to the main study. In addition to monitoring recruitment against projected targets, a qualitative study was embedded within the pilot phase to identify barriers to and facilitators of recruitment from the perspectives of primary care staff ($n = 9$) and patients ($n = 10$), and to pilot the qualitative topic guides. The following changes were made at the end of the pilot phase to facilitate recruitment:

- Patient information was streamlined, and clarification was provided on when to make an appointment and on rescue packs.
- The inclusion criteria were modified slightly (see *Appendix 1*, *Table 31*).
- The baseline case report forms (CRFs) were simplified.
- Guidance was provided to practices on which tasks could be delegated to members of the primary care team other than the treating clinician.
- Owing to the more sensitive instrument becoming available at the time, the EuroQol-5 Dimensions, three-level version (EQ-5D-3L), used during the internal pilot, was replaced with the EuroQol-5 Dimensions, five-level version (EQ-5D-5L).

Participants

During the main study (September 2015–February 2017), a total of 96 general practices in England and Wales were opened to recruitment at some point. Not all of these sites were able to recruit; not all were open during the whole study period and some sites were closed and new sites opened.

Participants were eligible if they had had an AECOPD for at least 24 hours but no longer than 21 days and did not meet any of the exclusion criteria, and they were recruited opportunistically while consulting in routine primary care. The eligibility criteria used in the pilot phase (see *Appendix 1*, *Table 32*) were modified slightly for the main trial (see *Appendix 1*, *Table 33*). The changes, which were made to facilitate recruitment, are summarised in *Table 31* (see *Appendix 1*).

Patients' informed consent to participate in the trial was obtained by the responsible clinician or an appropriately trained member of the practice team or a researcher. After this consent was obtained, data and sample collection were undertaken before the participants were remotely randomised to either the intervention or usual-care arm. Participant flow in the trial is summarised in *Figure 1*.

Trial interventions

Intervention arm (C-reactive protein point-of-care test)

Participants randomised to the intervention arm had a CRP POCT measurement to help guide initial antibiotic prescribing decisions for their AECOPD. This was used in addition to usual clinical assessment. Clinicians were asked to use the CRP POCT during all primary care AECOPD consultations that occurred during the 4 weeks following randomisation for those participants randomised to the intervention arm.

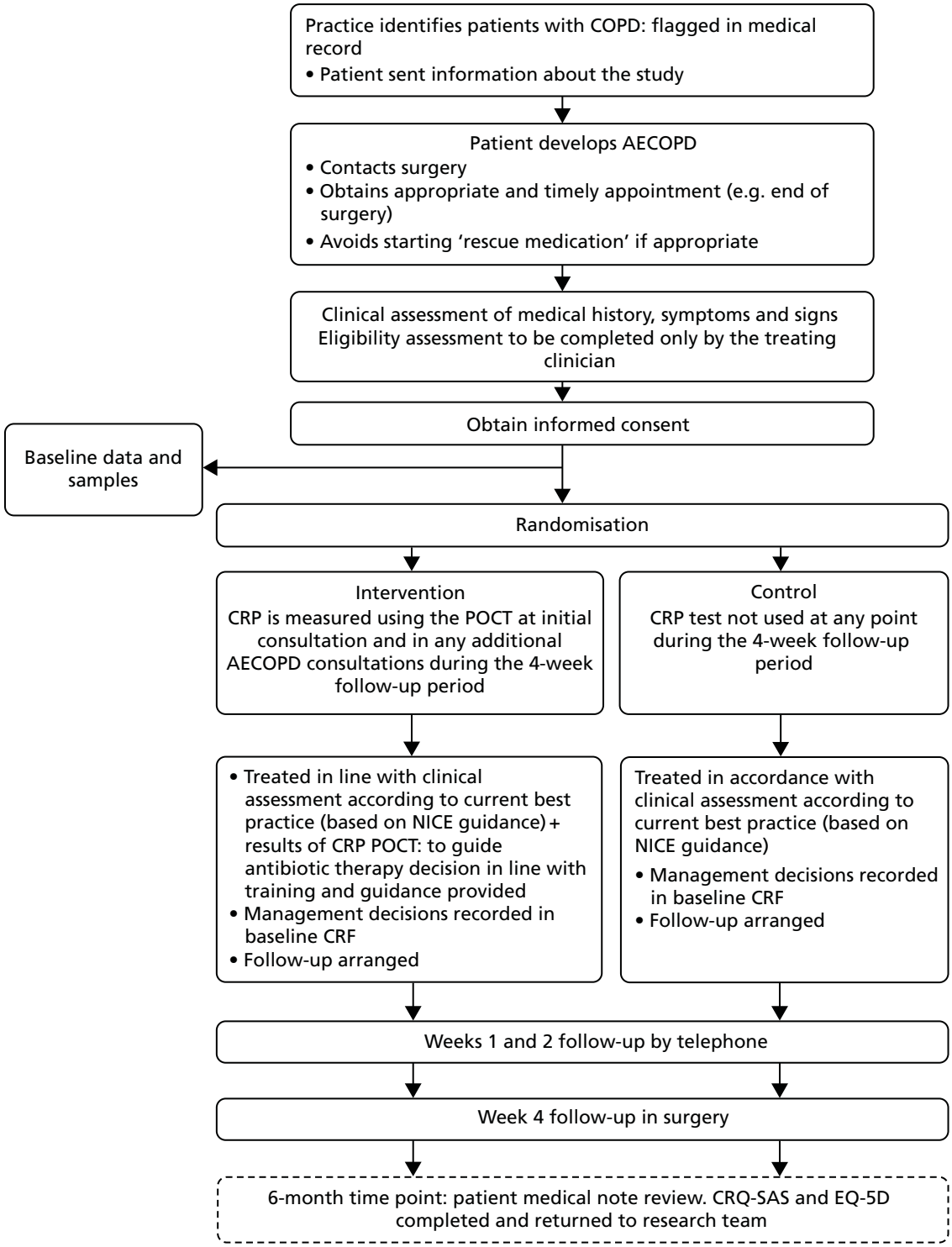

FIGURE 1 Participant flow diagram. NICE, National Institute for Health and Care Excellence. Reproduced from Bates *et al.*[38] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/.

Participating general practices were provided with a desktop CRP POCT Afinion device [Alere Afinion™ AS100 Analyzer, Alere Inc. (now Abbott Diagnostics), IL, USA] and CRP cartridges, and trained to use the device. This POCT required 1.5 µl of capillary blood (from a finger prick) and took < 4 minutes to provide a quantitative result. Other validated CE (Conformité Européene)-marked POCT devices and CRP cartridges giving a quantitative result within the range of the Alere Afinion POCT and requiring a similar volume of

blood from a finger prick were also eligible to be used in the study when a practice preferred to use a CRP POCT they were already using and that was quality controlled. Only two practices used a device other than the Alere Afinion. Clinicians in participating general practices (e.g. GPs, nurse practitioners, practice nurses and health-care assistants) were provided with study-specific training, which included guidance for the clinical prescribers on interpreting CRP results in the context of AECOPD (*Box 1*).

BOX 1 Guidance for interpreting CRP results

C-reactive protein 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, comorbidities, 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 an increased risk of complications:

- severe COPD (GOLD grade 3)
- past history of severe exacerbations (requiring hospitalisation)
- significant comorbidities (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 in bacterial infections
- try to obtain a sputum sample to objectively assess sputum purulence when 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.

C-reactive protein measurement

CRP level of < 20 mg/l

Antibiotics are unlikely to be beneficial and usually should not be prescribed.

CRP level of 20–40 mg/l

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.

C-reactive protein guidance

CRP level of > 40 mg/l

Antibiotics are likely to be beneficial. Consider prescribing antibiotics unless the patient is assessed as being at a lower risk of complications and unlikely to have a bacterial infection (no increased sputum purulence and no features suggesting severe exacerbation).

GOLD, Global Initiative for Chronic Obstructive Lung Disease.

The guidance was based on a review of evidence including data from our recently published placebo-controlled trial of antibiotics for patients with acute exacerbations of mild to moderate COPD.[24] A cut-off point of 48 mg/l of CRP had previously been shown to distinguish pneumonia from non-consolidative exacerbations,[39] and in our trial group we found that benefit from antibiotics was largely confined to those with a CRP level of > 40 mg/l.[24] We emphasised that CRP can take up to 24 hours to rise in a AECOPD, so duration of illness should be taken into account when interpreting the result. Our guidance, therefore, took a conservative approach and included cut-off points of < 20 mg/l, 20–40 mg/l and ≥ 40 mg/l, and placed greater emphasis on not prescribing antibiotics for those participants with a low level of CRP.

Control arm (usual care)

Participants allocated to usual care did not have a CRP POCT as part of the management of their AECOPD at any time during their participation and were managed according to usual care alone. All participating sites were provided with information on current best practice for managing AECOPD, which included a brief summary of National Institute for Health and Care Excellence (NICE) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidance delivered via the study-specific site initiation guidance, training and the PACE trial website (see *Report Supplementary Material 1*). No other specific guidance or instructions were given to clinicians in relation to the management of participants randomised to the usual-care arm.

Data collection

A summary of data collection is provided in *Table 1*. All data, including sensitive and personal data, were handled in accordance with the Data Protection Act 1998[40] and the subsequent General Data Protection Regulation 2016.[41] Paper CRFs were completed at all time points and then entered into the database by a member of the trial team. The database was built with internal validations and range checks. Queries arising during data entry were referred back to the site. Self-evident correction rules were developed during the trial in response to common errors of CRF completion. Central data monitoring was conducted throughout the trial, and a 10% quality control of all manually entered data was undertaken periodically. Following data cleaning, the data sets were extracted from the database, checked to ensure consistency with the paper CRFs and then provided to the statistician for analysis. All data will be retained for 15 years post trial closure in line with Cardiff University's procedures.

Baseline appointment

Baseline data collected included the number of days the participant reported experiencing AECOPD symptoms, medical history and clinical examination results (e.g. temperature, pulse, oxygen saturation, evidence of tachypnoea, crackles, wheezes, diminished vesicular sounds and evidence of consolidation). The clinicians responsible for managing the participant recorded the participants' clinical findings. The collection of additional data could be conducted by a suitably trained member of the practice team.

A sputum sample (when participants were able to produce sputum) and a throat swab sample (using a charcoal swab) were obtained from participants at the baseline appointment (prior to randomisation) for bacterial and biological analyses. The recruiting clinicians recorded the colour of the participant's sputum according to a BronkoTest© (London, UK) chart.[42] The BronkoTest is a colour chart that can be used by patients and clinicians to assess the colour of sputum to more effectively manage exacerbations of COPD. It is based on choosing one of five colours, and has been shown to correlate with the presence of bacterial pathogens in sputum.[43] If it was not possible to obtain sputum, participants were asked to estimate the current colour of their sputum based on a BronkoTest chart. These samples were appropriately packaged and sent to a local microbiology laboratory using first-class Royal Mail (London, UK) safe boxes at ambient temperature.

Participants were asked to self-complete the CCQ[44] and the EuroQol 5-Dimensions (EQ-5D) questionnaire[45–48] at their baseline appointment (prior to randomisation). The EQ-5D-3L was used for the 1-, 2- and 4-week follow-up assessments for the first 60 participants recruited; thereafter (and for all 6-month follow-ups),

TABLE 1 Baseline and follow-up data collected

Assessment	Time point				
	Baseline appointment	1 week (telephone call)	2 weeks (telephone call)	4 weeks (face to face)	6 months
Assessment of eligibility	✗				
Written informed consent	✗				
Contact details	✗				
Medication history	✗				
Temperature	✗				
Oxygen saturation	✗				
Antibiotic prescribing	✗				✗ (NS)
Antibiotics prescribed in the 12 months prior to study inclusion					✗ (NS)
Spirometry results (prior to inclusion or within 6 months post inclusion if no pre-inclusion results are available)					✗ (NS)
Most recent eosinophil count prior to inclusion					✗ (NS)
Other prescribed medications for current illness	✗				
CRP level[a]	✗				
CCQ	✗	✗	✗	✗	
EQ-5D	✗	✗	✗	✗	✗ (P)
Sputum sample and throat swab	✗			✗	
4-week return visit date	✗				
Antibiotics use		✗	✗	✗	✗ (NS)
Other medications for AECOPD		✗	✗	✗	
Adverse effects		✗	✗	✗	
Adherence to use of POCT	✗	✗	✗	✗	
Smoking history		✗			
Time off paid work				✗	
Diagnosis of pneumonia (since baseline appointment)				✗	
Health-care contact and use				✗	✗ (NS)
Mortality[b]				✗	✗ (NS)
CRQ-SAS					✗ (P)

NS, notes search; P, post.

a Only for patients randomised to the POCT arm.

b Deaths during the 4-week follow-up period only will be reported as serious adverse events.

the EQ-5D-5L was used. CRP test results were recorded for those randomised to the intervention arm. Antibiotics prescribing and other management decisions were recorded for all participants following randomisation (as well as the outcome of the test result for those allocated to the intervention arm).

Follow-up data collection

Follow-up included telephone calls at 1 and 2 weeks, and a face-to-face consultation at 4 weeks post randomisation. In addition, the CRQ-SAS[49] and the EQ-5D-5L were posted to participants for them to complete and return, using the provided and stamped addressed envelopes, to the study team at 6 months.

1- and 2-week telephone follow-up

A member of the trial team telephoned participants at weeks 1 and 2 to collect outcome data (see *Table 1*). Time windows for these data collection points were set at – 1/+ 2 working days for the 1-week follow-up and – 1/+ 7 working days for the 2-week follow-up.

4-week face-to-face visit

A 4-week face-to-face appointment at the general practice was arranged at the time of the baseline appointment. Appointments were conducted by a member of the clinical team in the general practice, or by a research nurse working for the local Clinical Research Network (CRN). The time window of the 4-week data collection was set at –3/+14 working days. *Table 1* reports the data captured at this time point. In addition, any further CRP tests carried out since the baseline appointment were recorded. Sputum and throat swab samples were obtained when possible, and the colour of the sputum was assessed against a BronkoTest chart. If it was not possible to obtain sputum, participants were asked to estimate the current colour of their sputum based on a BronkoTest chart. These samples were sent to a local microbiology laboratory, as at baseline. If a successful appointment did not take place at week 4, the study team contacted the participant by telephone to obtain a minimum data set, including antibiotic consumption during the third and fourth week after randomisation, health-care resource use, diagnosis of pneumonia and completion of the CCQ and EQ-5D questionnaires. Minimum data set questions for the 1- and 2-week follow-up telephone calls were completed at the 4-week assessment if these had not already been completed.

Collection of relevant data from electronic medical records at 6 months

The data ascertained at the 6-month notes reviews are presented in *Table 1*.

Patient self-reported Chronic Respiratory Disease Questionnaire Self-Administered Standardized and EuroQol 5-Dimensions, five-level version at 6 months

Participants were sent a copy of the CRQ-SAS and EQ-5D-5L at 6 months post randomisation. The trial team telephoned participants 1 and 2 weeks after the due date to remind them to complete and return the questionnaire by post, or to offer to complete these instruments over the telephone.

Adverse events

Hospitalisation was considered an expected event in this patient population and this information was collected and reported as part of routine follow-up. All other events fulfilling the definition of a serious adverse event (SAE), including death, that occurred between the time of consent and the 4-week follow-up, were reported to the co-ordinating research centre within 24 hours of the site becoming aware of the event.

Microbiological assessment

Sputum (if available) and throat swab samples were obtained at the baseline appointment visit and at the face-to-face visit at week 4. Samples obtained were sent to the Specialist Antimicrobial Chemotherapy Unit, Public Health Wales, at the University Hospital of Wales.

Not all participants were able to produce a sputum sample on request and, therefore, we expected a lower return rate for these samples than for the throat swab samples at both baseline and week 4.

Sputum sample appearance (including colour and consistency) was noted at the laboratory, and all sputum samples were processed using the laboratory's standard operating procedures. Potential pathogenic bacteria (including *S. pneumoniae*, *Haemophilus influenzae/H. parainfluenzae*, *Moraxella catarrhalis, Pseudomonas* species, Enterobacteriaceae and *Staphylococcus aureus*) were identified from sputum samples using matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry, and semiquantitative counts were recorded. Antimicrobial susceptibilities were performed on relevant bacterial species from sputum samples by disc diffusion using European Committee on Antimicrobial Susceptibility Testing (EUCAST) methodology and break points. Throat swabs (charcoal) were added to tryptone soya broth (BO0351Y, Oxoid, Basingstoke, UK) and 50 µl was spiral plated onto a range of non-selective plates and selective plates for identification purposes [e.g. Columbia blood agar with optochin discs, chocolate agar with bacitracin, *Pseudomonas* agar with cetrimide, fucidin and cephaloridine plus Iso-Sensitest™ agar (CM0471, Oxoid, Basingstoke, UK) with 5% defibrinated horse blood (TCS Biosciences, Buckingham, UK)] without and with the following antimicrobials: penicillin, third-generation cephalosporins, doxycycline, levofloxacin and clarithromycin at concentrations consistent with EUCAST break points. Total bacterial counts of commensal organisms were recorded on non-selective and selective agars; proportional quantification of resistant isolates was determined from the selective media. All isolated pathogens, sputum samples and the remaining broth from throat swabs were stored at –80 °C.

Nucleic acid was extracted from sputum samples using the Nuclisens® easyMAG® system (bioMérieux, Basingstoke, UK) and then analysed with the Luminex NxTAG® Respiratory Pathogen Panel (Luminex, Hertogenbosch, the Netherlands) for a variety of viral and bacterial pathogens.

Outcome measures

The co-primary outcome measure comprised:

1. Antibiotic consumption for AECOPD at any point during the 4 weeks post randomisation. Antibiotic consumption (rather than prescribing or dispensing) is the driver of antimicrobial resistance and was, therefore, selected as the outcome measure. With regard to the timing of this primary outcome, antibiotics consumed within 4 weeks of presenting with an AECOPD are likely to be related to the AECOPD and, therefore, using this time frame is more conservative in terms of demonstrating a reduction in antibiotic use related to the intervention. Data on antibiotic consumption were captured by participant self-report during the telephone interviews at weeks 1 and 2, and at the face-to-face interview at week 4. This was a binary outcome with a cut-off point of any consumption/no consumption.
2. COPD health status as measured with the CCQ via telephone interview at 2 weeks. The CCQ is a patient-centred health status measure that has been well validated, is widely used in patients with COPD and has a well-described minimal clinically important difference.[50] The CCQ is a brief questionnaire and, therefore, less burdensome to patients, and it is possible to use it with a recall period of 24 hours. CCQ scores range from 0 to 6 points, and the minimal clinically important difference is 0.4. CCQ was selected as a co-primary outcome to evaluate whether or not the intervention resulted in a meaningful reduction in antibiotic consumption (compared with usual care) without making COPD health status worse.

A 4-week time window was selected for the antibiotic consumption outcome to measure consumption of antibiotics prescribed at the initial consultation, and also antibiotics that were prescribed for the AECOPD in question but were initiated or prescribed at a later date. The CCQ outcome was measured at 2 weeks post randomisation as this is the time when most patients would be expected to have recovered and, therefore, the point at which a difference would be most indicative of delayed recovery.

Sample size

The study aimed to have sufficient power to detect a 15% reduction from an estimated 70% of patients who consume antibiotics for the AECOPD during the 4 weeks following randomisation.[9] Trials using CRP testing to reduce antibiotic prescribing for LRTI have resulted in absolute reductions in antibiotic prescribing in the region of 13–22%.[33,34,51] Even relatively small changes in prescribing are likely to have beneficial effects on bacterial resistance at a population level.[15] Detecting a difference in proportions between 0.70 and 0.55 at the 5% alpha and with 90% power required a total of 434 participants, inflated to 544 participants to account for the loss to follow-up of approximately 20% of participants. In addition, we aimed to have sufficient power to demonstrate that participants managed with the CRP POCT are no worse (non-inferior), compared with those managed without the CRP POCT, in terms of their COPD health status measured with the CCQ 2 weeks post randomisation. Assuming an expected difference between the arms of zero, a non-inferiority margin of 0.3 (this is lower than the lowest minimal clinically important difference of 0.4) and a common standard deviation (SD) of 1.1,[50] based on a one-sided alpha of 5% and 90% power, the study needed 462 participants, inflated to 580 participants to account for the loss to follow-up of approximately 20% of participants.

Formulating our overall hypothesis using the intersection–union test,[52] we aimed to carry out our individual sub-hypothesis tests at the 5% level and, if both were significant, conclude overall significance at the 5% level. Power will be affected by the level of correlation between the two outcomes and their corresponding effect sizes. The impact on overall power is at its greatest when there is zero correlation between outcomes and the effect sizes are identical (when this is the case, the overall power is the product of the powers for testing each individual sub-hypothesis).[53,54] Overall power decreases with increasing correlation between the outcomes and with greater difference in effect sizes. We did not expect our effect sizes to be similar, as our co-primary outcomes are two very different constructs (i.e. not two patient-reported outcome measures that are likely to yield similar effect sizes). We also anticipated that the outcomes would not be entirely independent (in those participants who do in fact require antibiotics, antibiotic consumption is likely to be related to COPD health status). We therefore aimed to recruit at least 650 participants to maintain an overall power between 81% and 90%.

Randomisation

Participants were remotely randomised, after giving their consent, using an online computerised randomisation system created by the Centre for Trials Research at Cardiff University. This was operational 24 hours a day. In addition, a telephone back-up was available from 8.30 a.m. to 6.30 p.m. if the online system failed or if the general practice had problems accessing the online site.

Participants were randomised in a 1 : 1 ratio to receive either usual care alone (control) or usual care with the addition of CRP POCT (intervention). Randomisation used minimisation, with a random element set at 80% to improve the integrity of the randomisation process. Anthonisen criteria (categorised as type 1, 2 or 3) were used as a minimisation variable to achieve balance with respect to COPD exacerbation severity. Remote allocation allowed the maintenance of allocation concealment from both the participant and the recruiting clinician up to the point of intervention, as this was an open study.

Statistical methods

Participant characteristics and clinical measures were summarised using frequencies and percentages, means and SDs or medians and interquartile ranges (IQRs), as appropriate. There was no planned interim analysis. All analyses have been presented as estimates of treatment effects (adjusted mean differences or odds ratios, as appropriate), with associated 95% CIs and *p*-values. The main trial analysis was based primarily on a modified intention-to-treat (MITT) population, which included all randomised participants who provided outcome data, regardless of protocol deviations or intervention received. Missing outcome data were imputed using multiple imputation to obtain a secondary analysis of the primary outcomes based on the full intention-to-treat (ITT) population. A complier average causal effect (CACE) analysis, which accounted for departures from randomised treatment while maintaining a comparison of groups as randomised, was also conducted on the primary CCQ analysis.[55] The conclusions drawn on the primary

CCQ analysis were based on both the MITT and the CACE analyses [i.e. the upper limit of the one-sided 95% CI (equivalent to the two-sided 90% CI) had to exclude 0.3 in both analyses for non-inferiority to be concluded].

All planned analyses were conducted using Stata (version 13.0; StataCorp, College Station, TX, USA) described in detail in a statistical analysis plan, which was finalised prior to database lock.

Primary analysis

Our first primary analysis was to compare the odds of consuming an antibiotic for an acute exacerbation during the 4 weeks following randomisation, in each trial arm, using logistic regression. Our second primary analysis was to compare the mean CCQ score between each trial arm using linear regression, with baseline CCQ scores included as a covariate and a one-sided 95% CI constructed to assess non-inferiority. We fitted two-level regression models (using the *mixed* and *melogit* commands) to account for clustering of participants within practices. Modelling assumptions were tested, with appropriate adjustments made in the presence of any violations. Missing primary outcome data were anticipated to be minimal, but were accounted for in sensitivity analyses using multiple imputation (using the *mi* commands), where we assumed that primary outcome data are missing at random given observed measurements. Further sensitivity analyses considered the impact that departures from the missing at random assumption may have on any conclusions that could be drawn (using the *rctmiss* command).

Our second primary analysis, testing the non-inferiority of management with CRP versus no CRP with respect to the CCQ, was based on our prespecified margin of 0.3. We prespecified that if the observed difference in CCQ was between 0.3 and 0.4 (0.4 is the minimal clinically important difference for the outcome), we would further reflect on differences found in antibiotic consumption and secondary outcomes (e.g. antibiotic resistance, EQ-5D) between the two trial arms before drawing any conclusions.

Secondary analysis

Secondary outcomes were analysed in a similar manner to the primary outcomes, with linear, logistic, Poisson and negative binomial regression models fitted as appropriate (for the last two, the *mepoisson* and *menbreg* commands were used). The majority of regression models accounted for clustering effects of participants within practices. The analysis of CCQ domains and EQ-5D (both health utility and health status variables) over time involved fitting a three-level model, with responses nested within participants within practices. The antibiotic resistant organism outcomes (for both sputum and throat swabs at 4 weeks) were compared between the arms using binomial regression (using the *binreg* command).

Subgroup analysis

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

- COPD severity (GOLD I/II/III/IV), from spirometry results (prior to inclusion or within 6 months post inclusion if no pre-inclusion results are available)
- the severity of COPD exacerbation (Anthonisen criteria type 1/2/3)
- the presence of a potentially pathogenic bacteria cultured from a sputum sample at baseline.

Sensitivity analysis

We determined whether or not the primary analyses were robust to the following sensitivity analyses:

- modifying the inclusion criteria following the internal pilot
- excluding participants on the basis of protocol violations
- accounting for antibiotic consumption over time (rather than considering it as one single binary variable).

Patient and public involvement

The PACE trial patient and public involvement (PPI) representatives were both co-applicants and advisors on PACE and members of the Trial Management Group. They were recruited through Cynnwys Pobl (Involving People, Wales) and had relevant training and experience of contributing to national and local committees seeking to improve care for COPD sufferers. Sadly, one of our PPI representatives passed away before the end of the study. During the development of the PACE trial proposal, PPI representatives attended development team meetings, discussed the proposed research with a COPD patient group and contributed to the design of the trial. They paid special attention to plans for approaching/recruiting participants and providing participant-facing study materials, ensuring that participating patients felt safe in the knowledge that, should their acute exacerbation indicate the need for antibiotics, these would be prescribed. They were also involved in reviewing and discussing our primary outcome in relation to the best method of assessing quality of life and recovery in AECOPD. As members of our Trial Management Group, they continued to play a pivotal role in the design and conduct of the study, and our remaining PPI representative assisted with the dissemination of this research.

Ethics approval and governance

Ethics approval for the trial was given on 15 September 2014 by the Research Ethics Committee (REC) for Wales (Wales REC 6), recognised by the United Kingdom Ethics Committee Authority (REC reference 14/WA/1106). All sites received research and development approval from the appropriate Health Boards and Clinical Commissioning Groups before commencing trial procedures. The trial was registered on 20 August 2014 with the International Standard Randomised Controlled Trial Registration Number ISRCTN24346473. Cardiff University acted as a sponsor for the trial.

A summary of the changes made to the original protocol is given in *Appendix 1*, *Table 35* (all outcome measures and changes to the outcome measures are shown in *Appendix 1*, *Table 30*).

Chapter 3 Clinical effectiveness results

Recruitment and participant flow

Ninety-six general practices across five research network hubs were open to recruitment at some point during the study period between January 2015 and February 2017. Ten of these practices did not recruit any participants.

It should be noted that completing screening logs is challenging for busy general practices, especially for patients with acute medical conditions. Not all of the clinicians working at each site participated in the study, worked full-time or were available to recruit each time they were on service. Fifty-six practices returned one or more screening logs, but, of these, only nine returned screening logs had data that were considered reliable (i.e. were regularly returned and consistently included details of participants' approach in addition to those recruited). Using data from these reliable returns, we estimate that 1988 patients were approached in total, with 1319 patients being eligible for inclusion in the study (approximately 66% of those approached).

Six hundred and fifty-three participants were recruited from 86 general practices.

Table 2 provides a breakdown of the number of sites and participants from each recruitment centre. Overall, practices recruited a median of five participants, with the number per practice ranging from 1 to 40 participants.

Three randomised participants withdrew from the study, including withdrawal of their consent for their data to be used, and one participant was randomised in error (with the recruiting clinician destroying their data). All subsequent analyses are based on a maximum of 649 participants. *Figure 2* provides details of recruitment and retention throughout the study.

TABLE 2 Participant recruitment and site participation across recruitment centres

Recruitment centre	Number of participants	Number of sites (general practices)	Number of participants per practice		
			Mean	Median	Minimum to maximum
Cardiff and South Wales	328	33	9.9	7.0	1 to 40
London	84	20	4.2	2.5	1 to 15
Oxford and Thames Valley	149	19	7.8	6.0	2 to 33
Norfolk	77	9	8.6	7.0	2 to 25
North-west coast	15	5	3.0	3.0	1 to 4
Overall	653	86	7.6	5.0	1 to 40

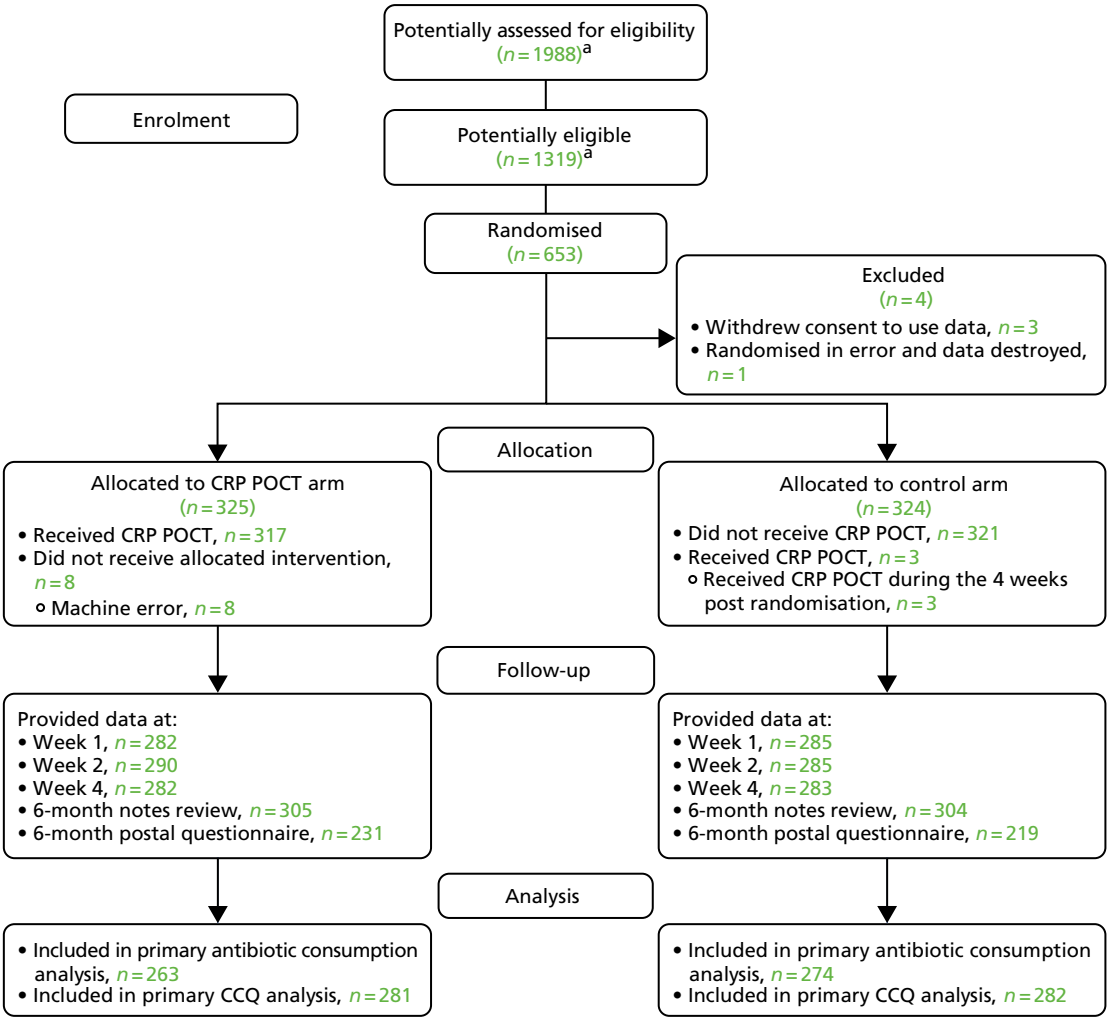

FIGURE 2 The Consolidated Standards of Reporting Trials (CONSORT) flow diagram. a, Number of participants assessed for eligibility based on screening log data from 9 out of 86 practices that returned reliable screening log data (i.e. were regularly returned and consistently included details of participants' approach in addition to those recruited). From these practices, 208 patients were approached (an average of 23 patients approached per practice), 138 patients (66.3%) were eligible and 109 patients were recruited. Potentially assessed for eligibility calculation: (208/9) × 86 = 1988. Potentially eligible calculation: (138/9) × 86 = 1319. The main reasons for patients' ineligibility were that they had recently used, or were currently using, antibiotics (28/70), or that they had already participated in the PACE trial (13/70). The main reasons because of which eligible patients were not recruited were because the patient declined (18/29) or because there was a lack of clinical time to recruit (9/29). Data are drawn from Butler *et al.*[56]

Baseline data

Participants in both arms were well matched at baseline. The key baseline characteristics, including participant demographics and presentation features, are provided in *Tables 3–5*.

Sputum bacteriological and virological profiles at baseline

At baseline, sputum sample bacteriology data were available for 195 usual-care participants and 202 CRP POCT participants (60.2% and 62.2% of randomised participants, respectively). Of the samples with potential pathogenic bacteria, 103 organisms were cultured from usual-care participants and 113 were in sputa from participants allocated to CRP POCT. There were 23 distinct potential pathogenic species identified in total. Potential pathogen profiles were similar between the arms (*Figure 3*). Baseline antibiotic sensitivity data for the three most frequently cultured potentially pathogenic species are presented in *Table 6*.

TABLE 3 Participant characteristics at baseline (1 of 2)

Variable	Trial arm											
	Usual care				CRP POCT				Overall			
	n	Mean (SD)	Median (IQR)	Minimum to maximum	*n*	Mean (SD)	Median (IQR)	Minimum to maximum	*n*	Mean (SD)	Median (IQR)	Minimum to maximum
Age (years)	324	68.3 (9.31)	68.5 (62.0 to 75.0)	40 to 92	325	67.8 (9.53)	68.0 (62.0 to 75.0)	41 to 90	649	68.1 (9.42)	68.0 (62.0 to 75.0)	40 to 92
Number of days with symptoms prior to consultation	324	7.1 (5.06)	6.0 (3.0 to 10.0)	1 to 21	325	6.8 (5.2)	5.0 (3.0 to 9.0)	1 to 28	649	6.9 (5.13)	5.0 (3.0 to 10.0)	1 to 28
Pack years (for current smokers)	92	47.8 (30.47)	41.6 (27.5 to 56.3)	5 to 165	95	41.0 (30.66)	36.0 (22.2 to 49.3)	3 to 162	187	44.4 (30.67)	40.0 (24.6 to 53.5)	3 to 165
CCQ symptoms score (points)	319	3.8 (1.09)	3.8 (3.0 to 4.5)	1.25 to 6.0	320	3.7 (1.14)	3.8 (3.0 to 4.5)	0.5 to 6.0	639	3.8 (1.11)	3.8 (3.0 to 4.5)	0.5 to 6.0
CCQ functional state score (points)	319	3.0 (1.45)	3.0 (2.0 to 4.0)	0.0 to 6.0	319	2.9 (1.54)	3.0 (1.8 to 4.0)	0.0 to 6.0	638	2.9 (1.49)	3.0 (1.8 to 4.0)	0.0 to 6.0
CCQ mental state score (points)	316	2.9 (1.60)	3.0 (1.5 to 4.0)	0.0 to 6.0	317	2.9 (1.64)	3.0 (1.5 to 4.0)	0.0 to 6.0	633	2.9 (1.62)	3.0 (1.5 to 4.0)	0.0 to 6.0
CCQ total score (points)	316	3.3 (1.11)	3.3 (2.4 to 4.2)	0.7 to 5.8	314	3.2 (1.16)	3.3 (2.4 to 4.1)	0.3 to 6.0	630	3.3 (1.14)	3.3 (2.4 to 4.1)	0.3 to 6.0
Overall health (EQ-5D)	289	48.3 (21.33)	50.0 (30.0 to 60.0)	0 to 100	288	48.6 (19.89)	50.0 (40.0 to 60.0)	0 to 98	577	48.5 (20.61)	50.0 (35.0 to 60.0)	0 to 100
Health utility (EQ-5D)	314	0.6 (0.27)	0.6 (0.5 to 0.8)	–0.4 to 1.0	316	0.6 (0.29)	0.7 (0.5 to 0.8)	–0.6 to 1.0	630	0.6 (0.28)	0.7 (0.5 to 0.8)	–0.6 to 1.0

Data are drawn from Butler *et al.*[56]

TABLE 4 Participant characteristics at baseline (2 of 2)

Variable	Trial arm, frequency (%)		Overall, frequency (%)
	Usual care	CRP POCT	
Male	173 (53.4)	162 (49.8)	335 (51.6)
Female	151 (46.6)	163 (50.2)	314 (48.4)
Heart failure	15 (4.6)	16 (4.9)	31 (4.8)
Coronary heart disease	59 (18.2)	55 (16.9)	114 (17.6)
Diabetes	54 (16.7)	50 (15.4)	104 (16.0)
Chronic kidney disease	32 (9.9)	27 (8.3)	59 (9.1)
Hypertension	143 (44.1)	124 (38.2)	267 (41.1)
Other chronic disease	70 (24.1)	85 (28.5)	155 (26.3)
Non-smoker	22 (7.9)	20 (7.1)	42 (7.5)
Ex-smoker	163 (58.4)	165 (58.7)	328 (58.6)
Current smoker	94 (33.7)	96 (34.2)	190 (33.9)
1/3 Anthonisen criteria	81 (25.0)	76 (23.4)	157 (24.2)
2/3 Anthonisen criteria	98 (30.2)	100 (30.8)	198 (30.5)
3/3 Anthonisen criteria	145 (44.8)	149 (45.8)	294 (45.3)
Current sputum colour according to BronkoTest (clinician-assessed if sputum obtained during consultation)			
1 (light/non-purulent)	48 (25.3)	59 (30.6)	107 (27.9)
2 (non-purulent)	47 (24.7)	39 (20.2)	86 (22.5)
3 (purulent)	36 (18.9)	50 (25.9)	86 (22.5)
4 (purulent)	53 (27.9)	37 (19.2)	90 (23.5)
5 (dark/purulent)	6 (3.2)	8 (4.1)	14 (3.7)
Current sputum colour according to BronkoTest (participant-assessed if sputum not obtained during consultation)			
1 (light/non-purulent)	14 (11.9)	14 (12.0)	28 (11.9)
2 (non-purulent)	18 (15.3)	22 (18.8)	40 (17.0)
3 (purulent)	28 (23.7)	22 (18.8)	50 (21.3)
4 (purulent)	23 (19.5)	27 (23.1)	50 (21.3)
5 (dark/purulent)	13 (11.0)	13 (11.1)	26 (11.1)
Unable to produce sputum	22 (18.6)	19 (16.2)	41 (17.4)
Sputum colour according to BronkoTest when not exacerbating (participant-assessed)			
1 (light/non-purulent)	126 (44.5)	130 (46.6)	256 (45.6)
2 (non-purulent)	74 (26.1)	88 (31.5)	162 (28.8)
3 (purulent)	32 (11.3)	23 (8.2)	55 (9.8)
4 (purulent)	12 (4.2)	9 (3.2)	21 (3.7)
5 (dark/purulent)	5 (1.8)	2 (0.7)	7 (1.2)
Unable to produce sputum	34 (12.0)	27 (9.7)	61 (10.9)

TABLE 4 Participant characteristics at baseline (2 of 2) (*continued*)

Variable	Trial arm, frequency (%)		Overall, frequency (%)
	Usual care	CRP POCT	
Crackles	162 (50.0)	158 (48.6)	320 (49.3)
Wheeze	167 (51.5)	171 (52.6)	338 (52.1)
Diminished vesicular sounds	82 (25.5)	71 (21.8)	153 (23.6)
Evidence of consolidation	8 (2.5)	11 (3.4)	19 (2.9)
Prescribed oral antibiotics in the past 12 months	198 (65.6)	205 (67.4)	403 (66.5)
Using regular inhalers prior to recruitment	290 (96.0)	289 (95.1)	579 (95.5)
Mobility			
No problems	64 (20.3)	79 (24.7)	143 (22.5)
Problems	252 (79.7)	241 (75.3)	493 (77.5)
Self-care			
No problems	172 (54.4)	202 (63.5)	374 (59.0)
Problems	144 (45.6)	116 (36.5)	260 (41.0)
Usual activities			
No problems	67 (21.2)	74 (23.1)	141 (22.2)
Problems	249 (78.8)	246 (76.9)	495 (77.8)
Pain/discomfort			
No problems	102 (32.4)	93 (29.2)	195 (30.8)
Problems	213 (67.6)	225 (70.8)	438 (69.2)
Anxiety/depression			
No problems	162 (51.3)	156 (48.8)	318 (50.0)
Problems	154 (48.7)	164 (51.2)	318 (50.0)
No bacterial growth in sputum/not analysed			
No growth	28 (14.4)	23 (11.4)	51 (12.8)
Insufficient sample	2 (1.0)	4 (2.0)	6 (1.5)
Sputum not processed	0 (0.0)	1 (0.5)	1 (0.3)
Potential bacterial pathogens in sputum			
Pure growth of pathogen	22 (11.3)	23 (11.4)	45 (11.3)
Mixed growth including pathogens	60 (30.8)	65 (32.2)	125 (31.5)
No potential bacterial pathogens in sputum			
Normal respiratory flora	83 (42.6)	85 (42.1)	168 (42.3)
Mixed growth of non-pathogens	0 (0.0)	1 (0.5)	1 (0.3)

Data are drawn from Butler *et al.*[56]

TABLE 5 Participant lung function parameters at baseline

Variable	Trial arm								Overall			
	Usual care				CRP POCT							
	n	Mean (SD)	Median (IQR)	Minimum to maximum	*n*	Mean (SD)	Median (IQR)	Minimum to maximum	*n*	Mean (SD)	Median (IQR)	Minimum to maximum
Ratio of FEV_1 to FVC	224	0.6 (0.13)	0.6 (0.5 to 0.7)	0.23 to 0.85	205	0.6 (0.12)	0.6 (0.5 to 0.7)	0.30 to 0.85	429	0.6 (0.13)	0.6 (0.5 to 0.7)	0.23 to 0.85
% predicted FEV_1	282	60.4 (20.73)	59.2 (45.0 to 74.0)	11.4 to 150.4	277	59.2 (19.33)	58.9 (45.0 to 71.6)	9.9 to 125.4	559	59.8 (20.04)	59.0 (45.0 to 73.0)	9.9 to 150.4
Ratio of FEV_1 to FVC of < 0.7 (% of those with a calculable ratio), frequency (%)	181		80.8		172		83.9		353		82.3	
Ratio of FEV_1 to FVC of ≥ 0.7 (% of those with a calculable ratio), frequency (%)	43		19.2		33		16.1		76		17.7	
Mild COPD (GOLD I), frequency (%)	20		11.1		18		10.5		38		10.8	
Moderate COPD (GOLD II), frequency (%)	100		55.6		93		54.1		193		54.8	
Severe COPD (GOLD III), frequency (%)	47		26.1		52		30.2		99		28.1	
Very severe COPD (GOLD IV), frequency (%)	13		7.2		9		5.2		22		6.3	

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.
Data are drawn from Butler *et al.*[56]

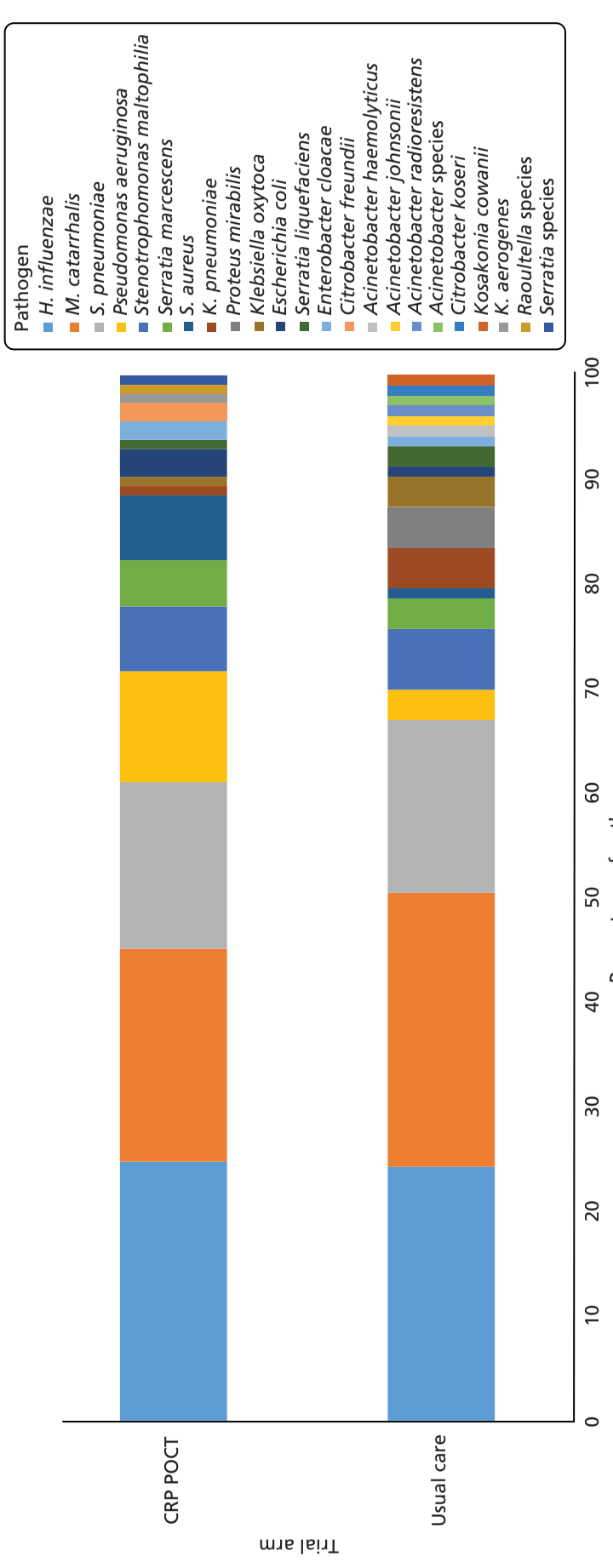

FIGURE 3 Potential bacterial pathogens from sputum samples at baseline. Usual care data based on 103 potential bacterial pathogens from 82 participants. CRP POCT data based on 113 potential bacterial pathogens from 88 participants.

TABLE 6 Antibiotic resistance in the most common potential pathogens cultured from sputum samples at baseline

		Trial arm					
		Usual care		CRP POCT		Overall	
Bacteria[a]	Antibiotic	Tested (*n*)	Resistant, *n* (%)	Tested (*n*)	Resistant, *n* (%)	Tested (*n*)	Resistant, *n* (%)
H. influenzae (*n* = 45)	Ampicillin	20	5 (25.0)	24	10 (41.7)	44	15 (34.1)
	Cefotaxime	20	0 (0.0)	24	0 (0.0)	44	0 (0.0)
	Ceftazidime	20	20 (100.0)	25	25 (100.0)	45	45 (100.0)
	Co-amoxiclav	20	5 (25.0)	24	7 (29.2)	44	12 (27.3)
	Erythromycin	20	20 (100.0)	25	25 (100.0)	45	45 (100.0)
	Tetracycline	20	0 (0.0)	24	0 (0.0)	44	0 (0.0)
M. catarrhalis (*n* = 44)	Ampicillin	22	22 (100.0)	21	21 (100.0)	43	43 (100.0)
	Cefotaxime	22	1 (4.5)	22	1 (4.5)	44	2 (4.5)
	Ceftazidime	0		0		0	
	Co-amoxiclav	22	0 (0.0)	22	0 (0.0)	44	0 (0.0)
	Erythromycin	22	3 (13.6)	22	1 (4.5)	44	4 (9.1)
	Tetracycline	22	0 (0.0)	22	0 (0.0)	44	0 (0.0)
S. pneumoniae (*n* = 36)	Ampicillin	15	5 (33.3)	10	1 (10.0)	25	6 (24.0)
	Cefotaxime	0		0		0	
	Ceftazidime	17	17 (100.0)	15	15 (100.0)	32	32 (100.0)
	Co-amoxiclav	15	5 (33.3)	10	1 (10.0)	25	6 (24.0)
	Erythromycin	18	5 (27.8)	18	2 (11.1)	36	7 (19.4)
	Tetracycline	18	3 (16.7)	18	3 (16.7)	36	6 (16.7)

a The *n* refers to the frequency of the corresponding potentially pathogenic species being cultured from sputum samples at baseline. *H. influenzae* is naturally resistant to ceftazidime and erythromycin. *M. catarrhalis* is naturally resistant to ampicillin. *S. pneumoniae* is naturally resistant to ceftazidime.

Antimicrobial discs were used for susceptibility testing of all sputum samples. All discs were supplied by Oxoid (Basingstoke, UK).

Both bacteriology and virology data from sputum samples at baseline were available for 190 usual-care participants and 196 CRP POCT participants. There was little difference between the arms regarding the general microbiological profile of sputum samples. Overall, no pathogens were detected in 95 out of 386 sputum samples (24.6%), bacterial pathogens only (i.e. no viral/atypical pathogens) were detected in 79 out of 386 cases (20.5%), viral/atypical pathogens only were detected in 123 out of 386 cases (31.9%), and both bacterial and viral/atypical pathogens were detected in 89 out of 386 cases (23.1%). Of those with viral/atypical pathogens, 137 viruses/atypical organisms were detected in samples obtained from usual-care participants and 117 in those allocated to CRP POCT. Ten distinct species were detected in total. Pathogen profiles were similar between the arms (*Figure 4*).

In total, 97.5% (317/325) of participants allocated to the CRP POCT arm reported receiving a CRP POCT during the recruitment consultation. For the remaining eight participants, a CRP POCT could not be carried out because of a machine error. Of the participants allocated to the usual-care arm, 13.6% (44/324) reported receiving a finger-prick blood test at some point within the 4 weeks following randomisation. However, 84% (37/44) of these reports of finger-prick blood testing were verified (by checking machine logs and 6-month notes reviews, and querying with the recruiting practice) as not being CRP tests. CRP testing was confirmed in three instances (all at the initial consultation) and unverified (i.e. no additional data to confirm or deny) in four instances. Therefore, the percentage of usual-care participants who received a CRP POCT was between 0.9% (3/324) and 2.2% (7/324).

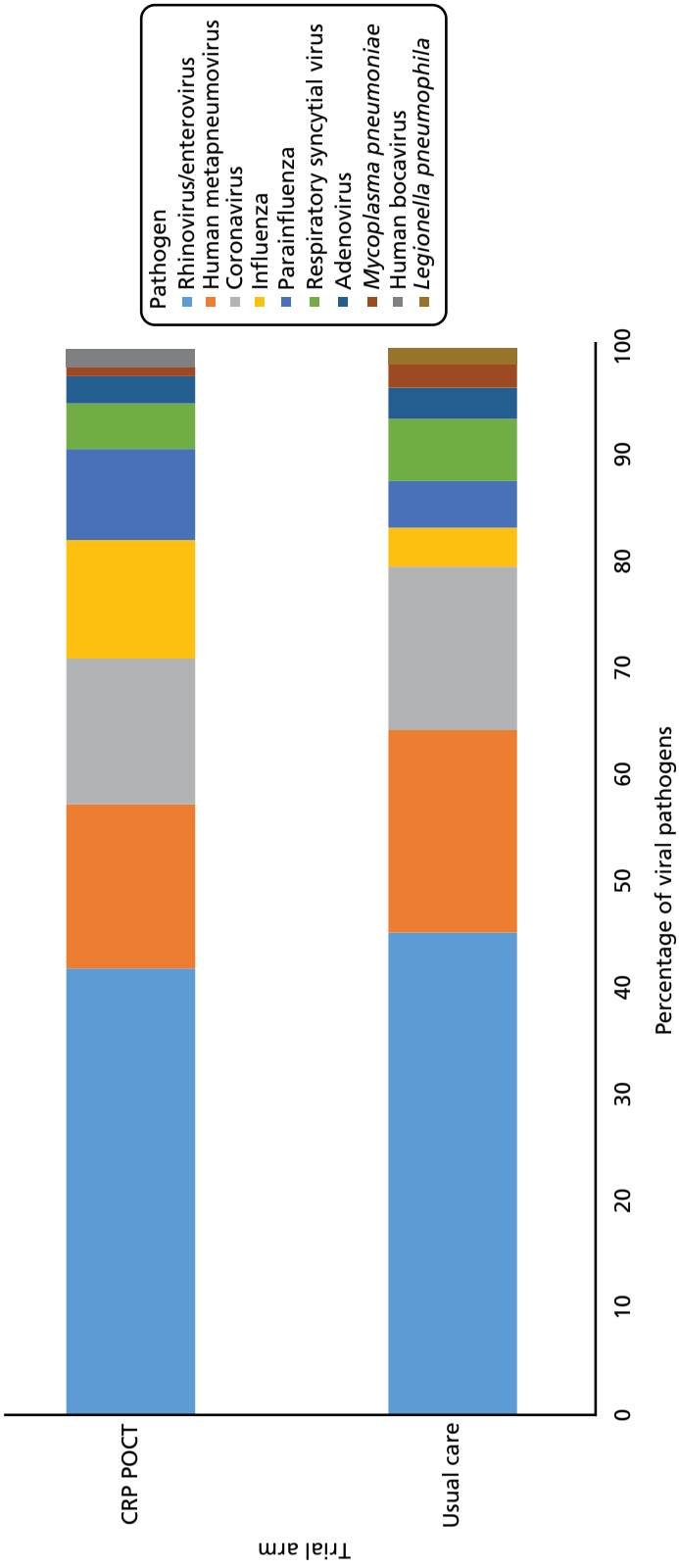

FIGURE 4 Viral and atypical pathogens from sputum samples at baseline. Usual-care data based on 137 viral/atypical pathogens from 109 participants. CRP POCT data based on 117 viral/atypical pathogens from 103 participants. Confirmation of CRP POCT testing.

Distribution of C-reactive protein values

For the 317 participants allocated to the CRP POCT arm and for those who were tested with a CRP POCT at the index consultation, the median CRP value was 6 mg/l (IQR 5–18.5 mg/l). Of those participants, 76.0% (241/317) had CRP values of < 20 mg/l, 12% (38/317) had CRP values in the intermediate category (20–40 mg/l) and 12% (38/317) had CRP values in the highest range (> 40 mg/l) (*Figure 5*).

Outcomes and estimation

Co-primary outcomes

Of the 649 participants randomised, 537 contributed to the primary analysis of antibiotic consumption (82.7%) and 563 contributed to the primary analysis of CCQ total score at 2 weeks post randomisation (86.7%).

The odds of consuming an antibiotic for AECOPD during the first 4 weeks following randomisation were 69% lower in participants allocated to the CRP POCT arm than in those in the usual-care arm (*Table 7*).

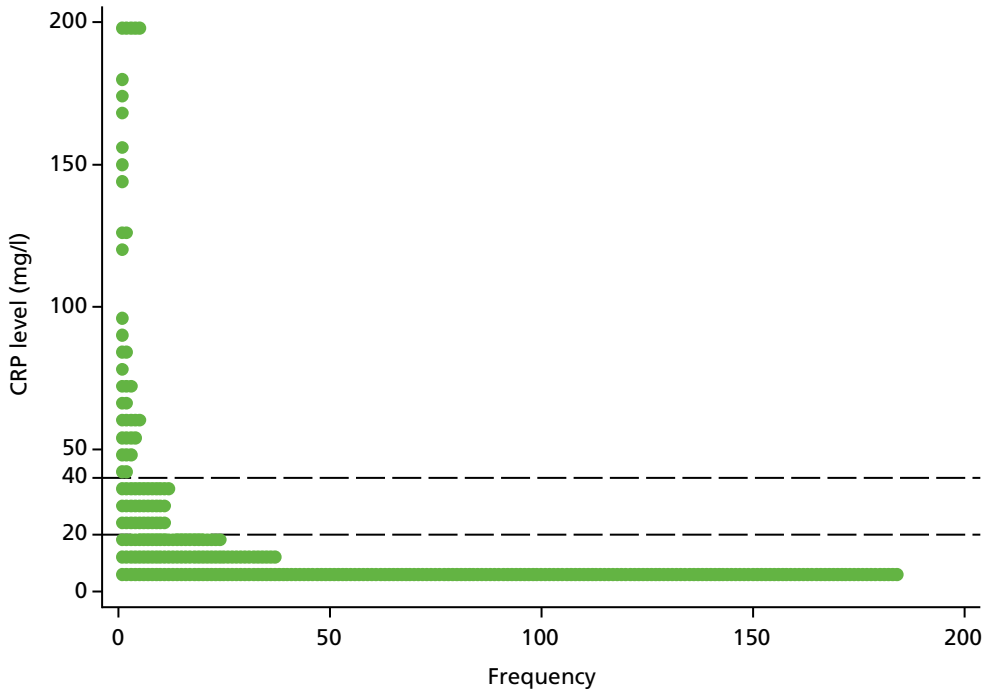

FIGURE 5 Dot plot of CRP levels. Censored observations are fixed at censored value (i.e. < 5 and > 200 are set to 5 and 200, respectively). The dashed lines are at $y = 20$ and $y = 40$ to distinguish between the three categories provided to clinicians as part of the intervention.

TABLE 7 Between-arm comparison of antibiotic consumption for AECOPD during the 4 weeks post randomisation

Outcome measure	Time point	Trial arm: Usual care *n*	Usual care Frequency (%)	CRP POCT *n*	CRP POCT Frequency (%)	AOR[a] (95% CI)	*p*-value	ICC
Antibiotic consumption for AECOPD	During the 4 weeks post randomisation	274	212 (77.4)	263	150 (57.0)	0.31 (0.20 to 0.47)	< 0.001	0.17

AOR, adjusted odds ratio; ICC, intraclass correlation coefficient.
a Ratio is CRP POCT/usual care. Adjusted for Anthonisen criteria. Clustering of participants within practices accounted for by fitting a two-level logistic regression model (analysis based on 537 participants within 82 practices). ICC calculated using $\pi^2/3$ estimator.

The adjusted mean difference in CCQ score was 0.19 (two-sided 90% CI –0.33 to –0.05) points lower in the CRP POCT arm than in the usual-care arm. The two-sided 90% CI for both CACE analyses ranged from –0.34 to –0.07 points. The upper limit of both CIs did not include the prespecified non-inferiority margin of 0.3, suggesting that a CRP-assisted management strategy is no worse than usual management (without a CRP POCT) according to COPD health status at 2 weeks (*Table 8*).

As the null hypotheses were rejected for both co-primary outcomes, our overall (composite) primary hypothesis can also be rejected, and we can conclude that we found evidence that a CRP-assisted management strategy results in reduced antibiotic use for patients presenting to primary care with AECOPD without having a negative impact on COPD health status at 2 weeks.

Secondary outcomes

The percentage of participants included in the analysis of secondary outcomes, based on data collected in the 4 weeks following randomisation, ranged from 74.0% (480/649) for the total number of days that antibiotics were consumed during the first 4 weeks outcome to 99.8% (648/649) for the antibiotic prescribing at the index consultation outcome. The percentage of participants included in the secondary outcome analysis of the CRQ-SAS domains, which were collected at 6 months via postal questionnaires, ranged between 61.5% for the dyspnoea domain (399/649) and 68.0% for the emotional function domain (441/649).

Medication use

Antibiotics were prescribed to 79 out of 241 participants with a CRP of < 20 mg/l (32.8%), 32 out of 38 participants with a CRP level between 20 and 40 mg/l (84.2%) and 36 out of 38 participants with a CRP level of > 40 mg/l (94.7%).

We found that the odds of consuming antibiotics for any reason during the 4 weeks following randomisation, receiving an antibiotic prescription at the initial consultation or receiving an antibiotic prescription during the 4 weeks following randomisation were lower in participants allocated to the CRP POCT arm than in those allocated to usual care. We found no evidence of any difference between the arms regarding the use of other COPD treatments during the 4 weeks following randomisation (*Table 9*). The between-arm analyses of the total number of days that antibiotics were consumed for AECOPD/any reason during the first 4 weeks following randomisation produced intervention effects consistent with the binary consumed/not consumed outcomes.

TABLE 8 Between-arm comparison of CCQ at 2 weeks post randomisation

Analysis set	Outcome measure	Time point	Trial arm				Adjusted mean difference[a] (90% CI)	ICC
			Usual care		CRP POCT			
			n	Mean (SE)	*n*	Mean (SE)		
MITT	CCQ (points)	Two weeks post randomisation	282	2.8 (0.07)	281	2.6 (0.07)	–0.19 (–0.33 to –0.05)	0.04
CACE 1							–0.20 (–0.34 to –0.07)	
CACE 2							–0.20 (–0.34 to –0.07)	

ICC, intraclass correlation coefficient; SE, standard error.

a Difference is CRP POCT minus usual care. Adjusted for Anthonisen criteria and baseline CCQ total score. Clustering of participants within practices accounted for by fitting a two-level linear regression model (analysis based on 563 participants within 83 practices). CACE 1 assumes that usual-care participants who have self-reported as having received a CRP POCT but have no further data to verify this have received it. CACE 2 assumes that those participants have not received a CRP POCT. CACE estimated using two-stage instrumental variables regression with cluster robust SEs used to account for clustering of participants within practices.

Data are drawn from Butler *et al.*[56]

TABLE 9 Between-arm comparisons of secondary outcome measures related to medication prescription or use

		Trial arm						
		Usual care		CRP POCT				
Outcome measure	Time point	*n*	Frequency (%)	*n*	Frequency (%)	AOR[a] (95% CI)	*p*-value	ICC
Antibiotic consumption for any reason	During the 4 weeks post randomisation	278	220 (79.1)	267	158 (59.2)	0.31 (0.20 to 0.48)	< 0.001	0.15
Antibiotic prescribing	During index consultation	323	225 (69.7)	325	155 (47.7)	0.31 (0.21 to 0.45)	< 0.001	0.21
Antibiotic prescribing	During the 4 weeks post randomisation	316	252 (79.7)	313	185 (59.1)	0.30 (0.20 to 0.46)	< 0.001	0.21
Use of other COPD treatments	During the 4 weeks post randomisation	290	268 (92.4)	290	263 (90.7)	0.79 (0.43 to 1.46)	0.453	0.14

AOR, adjusted odds ratio; ICC, intraclass correlation coefficient.
a Ratio is CRP POCT/usual care. Adjusted for Anthonisen criteria. Clustering of participants within practices was accounted for by fitting a two-level logistic regression model. ICC was calculated using $\pi^2/3$ estimator.

Potential medication side effects, consultations with primary/secondary care and pneumonia diagnoses

Symptoms commonly attributed as adverse effects from antibiotics and other COPD treatments were reported by 264 out of 289 participants in the usual-care arm (91.3%) and 255 out of 285 participants in the CRP POCT arm (89.5%) during the 4 weeks following randomisation [adjusted odds ratio (AOR) 0.79, 95% CI 0.44 to 1.39; $p = 0.410$]. There was no evidence of a difference between the arms regarding primary/secondary care consultations for any reason during the 6 months following randomisation (AOR 1.39, 95% CI 0.46 to 4.15; $p = 0.559$), or pneumonia diagnoses at 4 weeks (AOR 1.57, 95% CI 0.28 to 8.84; $p = 0.608$) or 6 months following randomisation (AOR 0.73, 95% CI 0.29 to 1.82; $p = 0.495$).

Patient-reported outcome measures

Table 10 describes the analyses of COPD health status (as measured with the CCQ) over time. For the total score, as well as the individual domains, there is a discernible reduction (improvement) in scores over the follow-up time periods. The adjusted mean difference (AMD) (averaged across follow-up time points) was lower (better) in the CRP POCT arm than in the usual-care arm for the total score (AMD –0.20, 95% CI –0.34 to –0.06; $p = 0.005$), symptom domain (AMD –0.19, 95% CI –0.34 to –0.05; $p = 0.010$) and function state (AMD 0.29, 95% CI –0.45 to –0.12; $p = 0.001$). There was no evidence of a difference for the mental state domain (AMD –0.08, 95% CI –0.27 to 0.10; $p = 0.372$). There was also no evidence of any differential intervention effect over time.

Table 11 describes the analysis of general health utility and health status over time (measured with the EQ-5D). For health utility, there was no evidence of any difference between arms averaged across follow-up time points (AMD 0.03, 95% CI –0.04 to 0.09; $p = 0.384$). Although there was some evidence of a difference in health utility across time in general (i.e. averaged across usual-care arm participants and CRP POCT arm participants), there was no evidence to suggest any differential intervention effect over time. There was a difference between arms in terms of general health status, with participants allocated to the CRP POCT arm reporting a health status score > 3 points higher than that of usual-care arm participants (AMD 3.12, 95% CI 0.50 to 5.74; $p = 0.019$). Health status generally improved over the follow-up time points, but, similar to the health utility measure, there was no evidence to suggest any differential intervention effect over time.

Table 12 describes the analysis of the COPD HRQoL at 6 months post randomisation (as measured by the four domains of the CRQ-SAS). There was no evidence to conclude any differences between arms for these outcomes. The AMDs were all small (ranging from –0.09 for the mastery domain to 0.15 for the emotional function domain), with no CIs containing values that would be considered to be clinically important (the literature suggests a minimally clinically important difference of between 0.4 and 0.5).

TABLE 10 Between-arm comparisons of CCQ scores over time

Outcome measure	Time point (weeks)	Trial arm, mean (SE)		Time point,[a] coefficient (95% CI)			Intervention effect[b]	
		Usual care	CRP POCT	Week 2	Week 4	*p*-value	Coefficient (95% CI)	*p*-value
CCQ total score (points)	1	2.8 (0.07)	2.6 (0.07)	–0.08 (–0.15 to –0.01)	–0.21 (–0.29 to –0.14)	< 0.001	–0.20 (–0.34 to –0.06)	0.005
	2	2.8 (0.06)	2.6 (0.07)					
	4	2.6 (0.07)	2.4 (0.07)					
CCQ symptom domain score (points)	1	3.2 (0.07)	3.0 (0.07)	–0.04 (–0.13 to 0.05)	–0.22 (–0.31 to –0.13)	< 0.001	–0.19 (–0.34 to –0.05)	0.010
	2	3.2 (0.07)	3.0 (0.07)					
	4	3.0 (0.07)	2.8 (0.07)					
CCQ function state score (points)	1	2.6 (0.08)	2.3 (0.08)	–0.11 (–0.19 to –0.02)	–0.14 (–0.23 to –0.05)	0.006	–0.29 (–0.45 to –0.12)	0.001
	2	2.5 (0.08)	2.2 (0.08)					
	4	2.5 (0.08)	2.2 (0.08)					
CCQ mental state score (points)	1	2.6 (0.09)	2.5 (0.09)	–0.14 (–0.24 to –0.03)	–0.39 (–0.49 to –0.28)	< 0.001	–0.08 (–0.27 to 0.10)	0.372
	2	2.4 (0.09)	2.4 (0.09)					
	4	2.2 (0.09)	2.1 (0.09)					

SE, standard error.

a Reference category is week 1.

b Adjusted mean difference (CRP POCT minus usual care) averaged across time points. Model adjusts for Anthonisen criteria and the corresponding CCQ score at baseline as a covariate. Clustering of responses within participants within practices is accounted for by fitting a three-level linear regression model (analysis based on up to 1675 responses among 608 participants within 83 practices).

TABLE 11 Between-arm comparisons of EQ-5D scores over time

Outcome measure	Time point	Trial arm, mean (SE)		Time point,[a] coefficient (95% CI)				Intervention effect[b]	
		Usual care	CRP POCT	Week 2	Week 4	Month 6	*p*-value	Coefficient (95% CI)	*p*-value
EQ-5D index value	Week 1	0.6 (0.01)	0.6 (0.01)	0.04 (0.00 to 0.08)	0.14 (0.11 to 0.18)	–0.05 (–0.09 to –0.01)	< 0.001	0.03 (–0.04 to 0.09)	0.384
	Week 2	0.6 (0.01)	0.6 (0.01)						
	Week 4	0.6 (0.01)	0.7 (0.01)						
	Month 6	0.6 (0.01)	0.6 (0.01)						
EQ-5D health status	Week 1	54.7 (1.24)	57.8 (1.26)	2.94 (1.13 to 4.75)	5.26 (3.40 to 7.11)	5.15 (3.16 to 7.14)	< 0.001	3.12 (0.50 to 5.74)	0.019
	Week 2	57.6 (1.24)	60.7 (1.25)						
	Week 4	59.9 (1.25)	63.0 (1.27)						
	Month 6	59.8 (1.31)	62.9 (1.32)						

SE, standard error.
a Reference category is week 1.
b Adjusted mean difference (CRP POCT minus usual care) averaged across time points. Model adjusts for Anthonisen criteria and the corresponding EQ-5D score at baseline as a covariate. Index values transformed by adding 0.6 to the original value (to make all responses positive) and then squaring. Clustering of responses within participants within practices is accounted for by fitting a three-level linear regression model (analysis of index values based on 2060 responses from 602 participants in 84 practices; analysis of health status values based on 1874 responses from 548 participants in 80 practices).

TABLE 12 Between-arm comparison of CRQ-SAS domains at 6 months post randomisation

Outcome measure	Time point	Trial arm				AMD[a] (95% CI)	*p*-value	ICC
		Usual care		CRP POCT				
		n	Mean (SE)	*n*	Mean (SE)			
CRQ-SAS dyspnoea domain	Six months post randomisation	193	4.2 (0.10)	206	4.3 (0.10)	0.06 (–0.20 to 0.33)	0.636	0.01
CRQ-SAS fatigue domain	Six months post randomisation	215	3.5 (0.11)	221	3.6 (0.11)	0.13 (–0.12 to 0.38)	0.295	0.11
CRQ-SAS emotional function domain	Six months post randomisation	216	4.3 (0.08)	225	4.4 (0.08)	0.15 (–0.04 to 0.34)	0.129	0.11
CRQ-SAS mastery domain	Six months post randomisation	214	4.3 (0.03)	221	4.2 (0.03)	–0.09 (–0.18 to 0.01)	0.065	0.00

ICC, intraclass correlation coefficient; SE, standard error.
a Difference is CRP POCT minus usual care. Adjusted for Anthonisen criteria. Clustering of participants within practices is accounted for by fitting a two-level linear regression model (analysis based on a maximum of 441 participants within 80 practices).

Sputum microbiology profile and outcomes at 4 weeks post randomisation

Sputum microbiological outcome analyses included 360 out of 649 samples for the comparison of the proportion with potentially pathogenic bacteria cultured from sputum at 4 weeks (55.5%) and 122 out of 649 samples for the comparison of the percentage of tested antibiotics to which at least one cultured, potentially pathogenic bacteria was resistant (18.8% of randomised participants; this analysis included only those with potentially pathogenic bacteria in sputum at 4 weeks).

At 4 weeks, sputum sample bacteriology data were available for 187 usual-care arm participants and 175 CRP POCT arm participants (57.7% and 53.8% of randomised participants, respectively). Among those with sputum bacteriology data, there was little difference between the arms regarding the microbiological profile. Potential pathogens (either pure or mixed) were found in 67 out of 187 samples from usual-care arm participants and in 62 out of 175 samples from CRP POCT arm participants (35.9% and 35.4%, respectively). Normal respiratory flora alone (i.e. no potential pathogens) was found in 42 out of 187 samples from usual-care arm participants and in 41 out of 175 samples from CRP POCT arm participants (22.5% and 23.4%, respectively).

Both bacteriology and virology data from sputum samples at 4 weeks were available for 178 usual-care arm participants and 167 CRP POCT arm participants (54.9% and 51.4%, respectively). There was little difference between the arms regarding the general microbiological profile of sputum samples. In 154 out of 345 participants, neither potential bacterial nor viral/atypical pathogens were detected (44.6%). Although just over one-fifth of participants provided a sample from which only a potential bacterial pathogen was detected (79/345, 22.9%), the majority of participants provided a sample from which a potential viral/atypical pathogen was detected alone (66/345, 19.1%) or in combination with a potential bacterial pathogen (46/345, 13.3%).

There was no evidence of any differences between the arms in terms of the presence of potentially pathogenic bacteria cultured from sputum at 4 weeks (AOR 0.97, 95% CI 0.63 to 1.50; $p = 0.905$) nor in the percentage of tested antibiotics to which at least one potentially pathogenic bacteria (cultured from sputum at 4 weeks) was resistant (*Table 13*).

Baseline throat swab sample data were available for 309 usual-care arm participants and 320 CRP POCT arm participants (95.4% and 98.8% of randomised participants, respectively). Resistance to antibiotics in commensal bacteria detected from throat swabs, expressed as the percentage of total bacteria load that grew on each antibiotic plate, was similar between arms (*Table 14*).

At 4 weeks, throat swab sample data were available for 270 usual-care arm participants and 267 CRP POCT arm participants (83.3% and 83.1% of randomised participants, respectively). Analysis of throat swabs at 4 weeks was based on 537 out of 649 participants (82.7%). There was no evidence of any differences between the arms in the percentage of the total bacterial load from throat swabs that grew on any of the five antibiotic plates (i.e. penicillin, levofloxacin, clarithromycin, doxycycline and extended-spectrum beta-lactamases) at 4 weeks (*Table 15*).

Sensitivity analyses

The conclusions drawn on the co-primary analyses were robust to all plausible assumptions made regarding missing outcome data, accounting for the modification of eligibility criteria following the internal pilot and excluding participants on the basis of protocol violations (see *Appendix 2*, *Tables 36–43* and *Figure 16*).

TABLE 13 Between-arm comparisons of sputum microbiology outcome (percentage of antibiotics to which at least one cultured, potentially pathogenic bacteria from sputum was resistant at 4 weeks)

		Trial arm									
		Usual care				CRP POCT					
Outcome measure	Time point	*n*	Mean (SE) number of antibiotics tested	Mean (SE) number of isolates non-susceptible to an antibiotic	Mean (SE) %	*n*	Mean (SE) number of antibiotics tested	Mean (SE) number of isolates non-susceptible to an antibiotic	Mean (SE) %	Adjusted risk (proportion) difference[a] (95% CI)	*p*-value
Percentage of tested antibiotics to which at least one cultured, potentially pathogenic bacteria (from sputum) was resistant	Four weeks post randomisation	64	17.2 (0.99)	8.0 (0.59)	47.1 (2.81)	58	17.5 (1.06)	8.7 (0.76)	48.1 (3.10)	0.04 (–0.03 to 0.11)	0.293

SE, standard error.
a Difference is CRP POCT minus usual care. Adjusted for Anthonisen criteria. Cluster robust SEs used to account for clustering of participants within practices.

TABLE 14 Resistance to antibiotics in commensal bacteria detected from throat swabs at baseline (expressed as percentage of total bacterial load that grew on each antibiotic plate)

	Trial arm											
	Usual care				CRP POCT				Overall			
Variable	*n*	Mean (SD)	Median (IQR)	Minimum to maximum	*n*	Mean (SD)	Median (IQR)	Minimum to maximum	*n*	Mean (SD)	Median (IQR)	Minimum to maximum
Penicillin	309	48.0 (37.92)	39.5 (10.9 to 87.5)	0 to 100	320	50.8 (37.30)	50.0 (12.3 to 90.0)	0 to 100	629	49.4 (37.60)	45.8 (11.4 to 88.9)	0 to 100
Levofloxacin	309	16.0 (25.28)	3.8 (0.4 to 18.1)	0 to 100	320	18.3 (28.05)	3.3 (0.2 to 25.0)	0 to 100	629	17.1 (26.73)	3.6 (0.3 to 20.3)	0 to 100
Clarithromycin	309	43.6 (36.72)	34.2 (8.6 to 78.6)	0 to 100	320	47.2 (36.74)	40.0 (11.6 to 85.9)	0 to 100	629	45.4 (36.75)	36.8 (10.6 to 80.8)	0 to 100
Doxycycline	309	30.9 (33.09)	16.7 (2.6 to 51.7)	0 to 100	320	31.9 (33.36)	20.3 (2.6 to 55.2)	0 to 100	629	31.4 (33.20)	18.6 (2.6 to 54.1)	0 to 100
ESBL	309	2.2 (11.62)	0.0 (0.0 to 0.0)	0 to 100	320	5.4 (20.5)	0.0 (0.0 to 0.0)	0 to 100	629	3.8 (16.81)	0.0 (0.0 to 0.0)	0 to 100

ESBL, extended-spectrum beta-lactamases.

TABLE 15 Between-arm comparisons of throat swab bacteriology outcomes (percentage of total bacteria load from throat swabs that grew on the antibiotic plate at 4 weeks)

Outcome measure	Time point	Trial arm: Usual care *n*	Usual care Mean (SE) %	CRP POCT *n*	CRP POCT Mean (SE) %	Adjusted risk (proportion) difference[a] (95% CI)	*p*-value
Penicillin	4 weeks post randomisation	270	54.0 (2.24)	267	55.8 (2.18)	0.02 (–0.04 to 0.08)	0.566
Levofloxacin			16.5 (1.55)		16.6 (1.59)	0.00 (–0.04 to 0.04)	0.958
Clarithromycin			48.9 (2.31)		47.4 (2.21)	–0.01 (–0.09 to 0.06)	0.703
Doxycycline			35.8 (2.19)		33.3 (2.14)	–0.02 (–0.09 to 0.04)	0.468
ESBL			4.7 (1.17)		3.6 (0.96)	–0.01 (–0.04 to 0.02)	0.512

ESBL, extended-spectrum beta-lactamases; SE, standard error.
a Difference is CRP POCT minus usual care. Adjusted for Anthonisen criteria. Cluster robust SEs used to account for clustering of participants within practices.

Modelling medication use over time showed that antibiotic consumption displayed the greatest between-arm difference between the index consultation and 1 week post randomisation (the time during which most antibiotics were prescribed), and consumption decreased over the 4-week follow-up period in both arms (see *Appendix 2*, *Tables 44* and *45* and *Figure 17*). The use of other COPD treatments decreased at a similar rate in both arms over the 4-week follow-up period (see *Appendix 2*, *Table 46* and *Figure 18*).

The mean number of primary care consultations during the 6 months following randomisation was 6.3 [standard error (SE) 0.28] for participants allocated to the usual-care arm and 6.6 (SE 0.29) for participants allocated to the CRP POCT arm. The adjusted incidence rate ratio was 1.04 (95% CI 0.92 to 1.18; $p = 0.504$). The mean number of secondary care consultations during the 6 months following randomisation was 1.7 (SE 0.12) for participants allocated to the usual-care arm and 1.6 (SE 0.11) for participants allocated to the CRP POCT arm. The adjusted incidence rate ratio was 0.96 (95% CI 0.79 to 1.17; $p = 0.719$). The mean number of primary and secondary care consultations combined was, therefore, a combination of the two separate consultation variables and similarly indicated insufficient evidence of a difference between the arms (see *Appendix 2*, *Figures 19* and *20* and *Table 47*).

Subgroup analyses

Table 16 provides model estimates for prespecified subgroup analyses conducted for the primary antibiotic consumption outcome.

There was no evidence of a differential intervention effect for participants who provided a sputum sample containing potentially pathogenic bacteria at baseline.

Although there was also insufficient evidence to conclude a differential intervention effect according to COPD severity, there were some descriptive differences between the arms. Antibiotic consumption was consistently different between the arms for participants with GOLD I, GOLD II and GOLD IV COPD. However, 28 out of 40 (70.0%) usual-care arm participants with GOLD III COPD consumed antibiotics for AECOPD, compared with 30 out of 44 (68.2%) CRP POCT arm participants with GOLD III COPD.

TABLE 16 Subgroup analyses for antibiotic consumption for AECOPD within 4 weeks post randomisation (primary outcome)

Subgroup analysis	Variable	AOR[a] (95% CI)	*p*-value
COPD severity (GOLD category) (*n* = 335)	Usual care	Reference category for trial arm main effect (i.e. effect of trial arm for GOLD I subgroup)	0.119
	CRP POCT	0.29 (0.06 to 1.38)	
	GOLD I	Reference category for COPD severity main effect (i.e. effect of GOLD subgroup for participants allocated to usual-care arm)	0.816
	GOLD II	1.39 (0.42 to 4.64)	
	GOLD III	0.91 (0.24 to 3.37)	
	GOLD IV	1.18 (0.19 to 7.13)	
	CRP POCT × GOLD I	Reference category for trial arm × COPD severity interaction	0.146
	CRP POCT × GOLD II	1.19 (0.21 to 6.73)	
	CRP POCT × GOLD III	4.04 (0.62 to 26.54)	
	CRP POCT × GOLD IV	0.39 (0.03 to 6.07)	
Severity of COPD exacerbation (Anthonisen criteria) (*n* = 537)	Usual care	Reference category for trial arm main effect (i.e. effect of trial arm for 1/3 features subgroup)	0.506
	CRP POCT	1.30 (0.60 to 2.81)	
	1/3 features	Reference category for severity of COPD exacerbation main effect (i.e. effect of severity of COPD exacerbation for participants allocated to usual-care arm)	< 0.001
	2/3 features	4.73 (2.13 to 10.48)	
	3/3 features	9.34 (4.13 to 21.13)	
	CRP POCT × 1/3 features	Reference category for trial arm × severity of COPD exacerbation interaction	< 0.001
	CRP POCT × 2/3 features	0.12 (0.04 to 0.35)	
	CRP POCT × 3/3 features	0.14 (0.05 to 0.39)	
Presence of potentially pathogenic bacteria cultured from sputum at baseline (*n* = 337)	Usual care	Reference category for trial arm main effect (i.e. effect of trial arm for no potential pathogenic bacteria subgroup)	< 0.001
	CRP POCT	0.20 (0.09 to 0.43)	
	No potential pathogenic bacteria	Reference category for presence of potentially pathogenic bacteria cultured from sputum at baseline main effect (i.e. effect of presence of potential pathogenic bacteria for participants allocated to usual-care arm)	0.773
	Potential pathogenic bacteria	1.14 (0.48 to 2.72)	
	CRP POCT × no potential pathogenic bacteria	Reference category for trial arm presence of potential pathogenic bacteria interaction	0.553
	CRP POCT × potential pathogenic bacteria	1.42 (0.45 to 4.49)	

a Models adjust for Anthonisen criteria (when it is not the subgroup of interest).

There was some evidence to suggest a differential intervention effect for antibiotic consumption by the severity of the COPD exacerbation (according to the Anthonisen criteria). *Figure 6* illustrates this differential effect, indicating that antibiotic consumption was similar between the arms for participants who met one out of the three Anthonisen criteria and differences were only observed for participants with two or more of the symptoms.

There was no evidence of any differential intervention effects for the primary CCQ outcome for any of the other prespecified subgroups (see *Appendix 2*, *Table 48*).

Adverse events

Serious adverse events were collected during the first 4 weeks following randomisation. During this period, two SAEs were reported. These were both events where study participants had died. Both participants were in the usual-care arm, and the SAEs were not deemed to be related to the intervention or to trial participation.

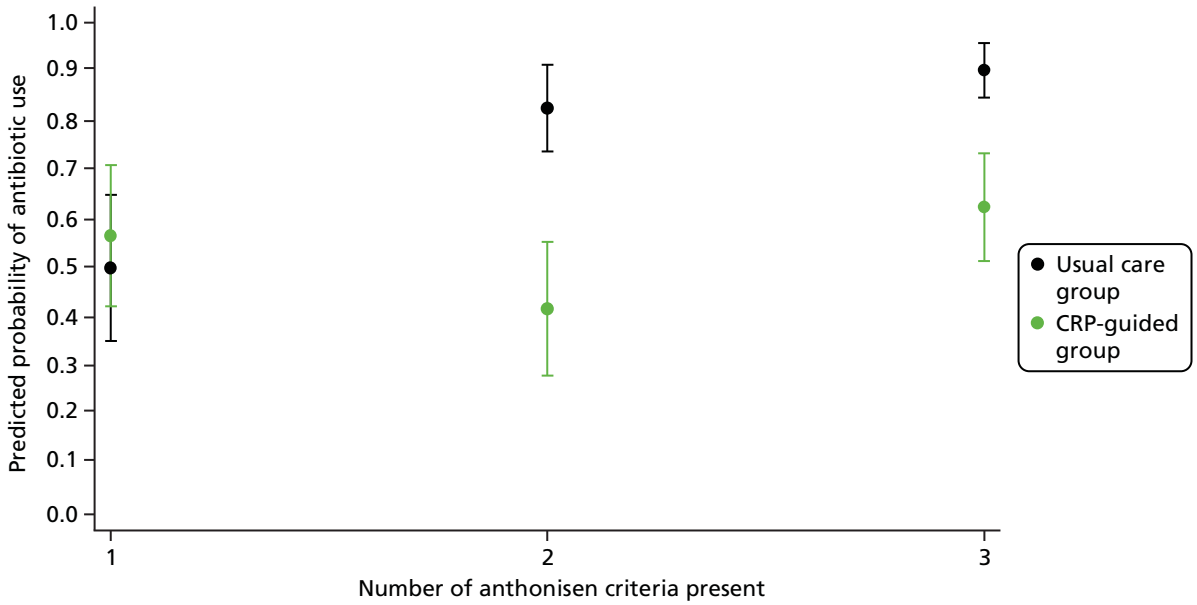

FIGURE 6 Differential effect of the intervention on the use of antibiotics during the first 4 weeks. Reproduced from *The New England Journal of Medicine*. Butler *et al.*, C-reactive protein testing to guide antibiotic prescribing for COPD exacerbations, 381, 111–20.[56] Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Chapter 4 Qualitative process evaluation

Aim

The aim of the qualitative process evaluation was to facilitate the interpretation of outcome results and assist with implementation planning.[57,58]

Methods

Setting and participants

Purposive sampling was used, with the aim of capturing a range of views and enabling saturation to be reached in framework analysis.[59] A sampling framework was used, with the aim of interviewing up to 20 patients in the CRP POCT trial arm and up to 20 members of the primary care teams who had carried out the CRP POCT with patients and/or used the CRP POCT result during consultations with patients. A sampling framework was used to ensure that views were captured from patients and members of the primary care teams in each of the regions where the PACE study took place (Wales, Oxford, London and Norfolk), and from approximately equal numbers of patients who had and had not been prescribed antibiotics at their initial consultation.

Procedure

Semistructured interviews were carried out over the telephone by a qualitative researcher. Topic guides (see *Report Supplementary Material 2*) focused on experiences of the management of AECOPD, the acceptability, implementation and potential mechanisms of the CRP POCT intervention and contextual factors that could influence future implementation.

Analysis

Interviews were audio-recorded and transcribed verbatim. NVivo 11 (QSR International, Warrington, UK) qualitative analysis software was used to assist coding. Data were 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.[60–62] 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.[63] 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.[60–62] This approach was used for the qualitative data gathered during the main trial phase, as opposed to a more traditional thematic analysis, to facilitate the identification of consensus and discrepancies in the themes emerging in different key groups (e.g. patients prescribed antibiotics vs. those who were not, GPs vs. other members of the primary care team) that would enable us to understand how contextual factors might interact with the acceptability and implementation of the CRP POCT.

During analysis, the qualitative researchers met regularly to discuss the coding, frameworks and themes as these developed. Data analysis was iterative, with the majority of analysis (familiarisation, development of framework and charting) taking place before the trial outcomes were known, in line with the Medical Research Council guidance on process evaluation.[58] The definition of data saturation used in this study was the point at which the ability to obtain additional new information had been attained and when further coding was not feasible.[64] Using the frameworks, the qualitative researchers (RP and HS) assessed whether or not the last five interviews with primary care staff and patients provided new information that would add to the theory being developed with regard to the mechanisms of impact for the intervention. On this basis, the judgement was made that data saturation had been achieved.

Results

Semistructured interviews were carried out with 20 patients and 20 primary care staff between October 2015 and March 2017. The interview participant characteristics are shown in *Table 17*.

The key themes identified through the framework analysis are summarised in *Table 18*.

Pseudonyms have been used alongside quotations from patients to protect anonymity. CRP readings and whether or not antibiotics were prescribed during the initial consultation (at the time of recruitment) are provided as the context for patient quotations.

Acceptability

All prescribers felt that the CRP POCT provided a useful piece of information, although several felt that this affected their decision only when there was some uncertainty about whether or not antibiotics were needed. Prescribers emphasised the importance of using clinical findings to guide antibiotic prescribing decisions, and recognised that CRP POCT testing provided additional information and was not a replacement for clinical skills:

> *I'm not daft enough to think that this test was a right/no thing, a yes/no thing and I know that clinical suspicion and judgment and history is far more important.*
>
> *General practitioner 2*

> *It's shown that we're not always right when we listen in, you know. There is a possibility that this may just be a viral crackle, as opposed to bacterial, but again it's very difficult without the reassurance of the, the CRP, to let the patient go away.*
>
> *Nurse practitioner 3*

TABLE 17 Characteristics of qualitative evaluation participants

Participants	*N*	Characteristics (*n*)	
Patients		***Prescribed antibiotics at index consultation***	***Not prescribed antibiotics at index consultation***
CRP level of < 20 mg/l	14	4	10
CRP level of > 20 mg/l	6	5	1
Total	20	9	11
Primary care staff		***Made prescribing decisions guided by CRP POCT result***	***Carried out the CRP POCT***
GPs	12	12	7
Nurse practitioners	5	5	5
Non-prescribers		***Made prescribing decisions guided by CRP POCT result***	***Carried out the CRP POCT***
Practice nurse	1	0	1
Research assistant	1	0	1
Pharmacist	1	0	1
Total	*20*	*17*	*15*

TABLE 18 Summary of key themes from the framework analysis of qualitative data

Main theme	Subtheme	Key points
Acceptability of the CRP POCT	General views of the CRP POCT	Patients and primary care staff generally thought that the CRP POCT was a useful addition to the consultation that would help guide antibiotic prescribing decisions. Primary care clinicians emphasised the importance of using the CRP POCT in addition to, not in place of, a thorough clinical assessment
Implementation of the CRP POCT	Technical aspects of the test	Primary care staff felt that the need for test cartridges to be refrigerated during storage and returned to room temperature before use, and the need for regular calibration of the machine, were barriers to using the CRP POCT in primary care
	Time	Primary care staff acknowledged the impact on consultation length that the use of the CRP POCT had, but felt that it was worthwhile
	Roll-out in routine practice	Patients and primary care staff were positive about the use of the CRP POCT in routine NHS care for the management of AECOPD. There were differences of opinion about whether the CRP POCT would be used for all patients with AECOPD, or for only those patients for whom there was uncertainty about the need for antibiotics based on clinical examination. The cost of the CRP POCT machine and cartridges was seen as a potential barrier to its use in NHS primary care services
Mechanisms of impact of the CRP POCT	Objective sign of illness	Patients and primary care staff felt that the CRP POCT provided an objective sign of illness that could help guide treatment. Prescribers felt that this increased their confidence in their antibiotic prescribing decisions
	Patient education tool	Primary care staff felt that the test was useful in educating patients about antibiotic use and antimicrobial resistance. Patients, however, had a limited understanding of these issues
	Reinforcing prescribers' decisions	Primary care staff perceived the CRP POCT result as being useful in reinforcing their decision about antibiotic prescribing when communicating with patients. Patients were generally passive in these consultations and did not report being involved with antibiotic treatment decisions. Continuity of care was viewed to be important by patients and clinicians in determining the quality of communication with regard to antibiotic prescribing decisions for AECOPD
Contextual factors	Attitudes towards antibiotics	Patient attitudes with regard to antibiotic use for AECOPD were varied, but many did not want to take antibiotics for AECOPD unless they were required. Primary care staff were aware of the need to reduce antibiotic use for AECOPD and acknowledged that patient attitudes varied and could influence prescribing decisions
	COPD routine care pathway	Anxiety around undertreatment through withholding antibiotics (including clinical outcomes and risk of litigation), and the use of 'rescue packs' that usually contain steroid and antibiotic medication that patients can start at home, could influence and be influenced by the use of the CRP POCT

Clinicians emphasised the importance of providing 'safety-netting' advice to patients if antibiotics were not prescribed, for example letting them know when they should reconsult or start medication that they had at home to reduce the risk of adverse clinical outcomes:

> *So other patients were you sort of think, well yes you have an exacerbation of your COPD, but I'm not sure if it's an infective one. It could be that you are just getting more symptoms. So I would have a discussion with them about starting steroids straight away, but actually delaying antibiotics for maybe 1 or 2 days and obviously giving them lots of safety advice and permission for them to start the antibiotics before then if they get a temperature, if they get increased sputum, and they feel that things are worsening, because obviously these are our frail, often frail and elderly patients who end up bouncing into hospital and that's the last thing that they want and that we want.*
>
> *Nurse practitioner 2*

One clinician described a case in which a CRP reading had been unexpectedly high and the effect that this had had on his perception of the value of CRP POCT testing:

> *I told my partner, who had seen this gentleman first this morning and I told him how high the CRP was. He was, he was as shocked as I was. Now it may be that this man has another reason for having a high CRP, you know, there may be something else going on other than infection and we're going to follow that up. But, but I would say that it would be, you know, the point-of-care testing would be an excellent thing to have in the surgery, because it can, you know, it can give you some information which, which you would not have on a clinical examination.*
>
> *General practitioner 3*

One of the aspects of the CRP POCT that primary care staff liked was that they felt that the test reassured patients, particularly when the CRP reading was low, and that the test demonstrated to the patient that a thorough examination had taken place:

> *They [patients] feel reassured that no antibiotics have been given and the doctor's actually checked that this was not necessary before he said 'no' to the antibiotics, rather than just saying 'no you don't need it'.*
>
> *General practitioner 1*

Patients felt that the CRP POCT was useful in rapidly deducing the severity of illness and/or the need for antibiotics:

> *I think it's a great idea to measure really sort of how ill you are and whether you really need more treatment or not.*
>
> *Participant 1, CRP < 20 mg/l, no antibiotics*

Patients were generally confident that the CRP POCT would help their doctors decide whether or not they needed antibiotics, but some felt that the test result was not consistent with their subjective experience:

> *I wasn't happy to be honest, because, simply because they said the test that was OK, and an ever slight inflammation which they took because of this blood test she found and she gave me 5 days of the steroids, but after the 5 days I was back to square one.*
>
> *Participant 2, CRP < 20 mg/l, no antibiotics*

Implementation of the C-reactive protein point-of-care test

Technical aspects of the test

Patients did not report any difficulties from a practical or technical perspective with clinicians' use of the CRP POCT, and they were satisfied with the way in which the CRP POCT was used. Primary care staff reported that they were able to use the CRP POCT with all patients randomised to the intervention arm, and that, in general, it was easy to use.

However, the need to refrigerate cartridges and allow time for them to return to room temperature before use and the need to regularly carry out control testing were both seen as burdensome and potential barriers to implementation. Some primary care staff felt that the CRP POCT would require an operational overhaul to make it simpler and faster to use during routine care:

> *I think that, you know, in theory that [using the CRP POCT in routine care] could be very good, but the only thing I would say is that because it's so cumbersome within the consultation clinicians won't use it, I'm just being honest with you, it takes, you know, 10 minutes to go and sort the machine and calibrate it, you know, how easy is that going to be?*
>
> *General practitioner 7*

The portability of the device was also identified as an important factor in the future development of the CRP POCT equipment:

> *I think it would be nicer if it was, you know in an ideal world, if it was a hand-held machine, so you could take it with you on a, on a home visit for instance, would be a useful.*
>
> *General practitioner 5*

Time

Patients reported that use of the test was 'quick' and that it did not cause any delays. The primary care staff described an 'investment' of time required to use the CRP POCT, and that using the machine did make consultations slightly longer. However, they felt that this was worthwhile:

> *I think where there was a great degree of uncertainty about what the right thing was to do, yeah there are definitely times when you'd be willing to invest that extra bit of time to do it.*
>
> *General practitioner 4*

Views about roll-out in routine practice

Patients and primary care staff had a positive view about whether or not the CRP POCT should be introduced into routine NHS care for patients with AECOPD:

> *I think it's an important test and if we, it's something I'd certainly want to explore in the future after the trial is finished, getting a CRP machine for the practice.*
>
> *General practitioner 5*

> *I think they're [GPs] doing their best, and I do think that the pinprick test is absolutely amazing and I should . . . I would like it to be done as a regular thing if you get a flare-up.*
>
> *Participant 3, CRP < 20 mg/l, not prescribed antibiotics*

Primary care staff discussed the advantages of using the test in routine care, mainly in terms of antibiotic stewardship and achieving better consistency in prescribing decisions:

> *So I think it may help to standardise the treatments that we offer, I definitely think it's a good idea, I think it's something that we should be doing more of, because I think we probably would end up prescribing less antibiotics because of it.*
>
> *Nurse practitioner 2*

Patients discussed the benefits of the test mainly in terms of reducing antibiotic use and saving money. Patients felt that the CRP POCT could 'help' doctors with their decisions and did not report any anxiety about having the test. Patients also recognised saving money and reducing antibiotic misuse as possible societal benefits of using the CRP POCT:

> *Helping decide if you need antibiotics or not, and I should imagine it would save money in the long run as well.*
>
> *Participant 4, CRP < 20 mg/l, no antibiotics*

Some clinicians said that they would use the CRP POCT for all patients presenting with AECOPD to 'increase their data'. This was understood to mean that they would use it as a learning tool to improve their ability to detect patients who are likely to need antibiotic treatment. Others felt that they would not use the CRP POCT for all patients, particularly when they felt confident in making a decision based on their

clinical judgement. Primary care staff felt that the CRP POCT would be introduced across a range of conditions in routine practice, rather than being used exclusively for patients with AECOPD:

> *I can really see that near point testing of CRP is a brilliant idea and I am sure that it is going to expand to lots of other things. I think patients really like it because it makes sense to them.*
>
> *General practitioner 6*

Primary care staff felt that the cost of the CRP POCT machine and cartridges was prohibitive under current funding arrangements, and that it would not be widely adopted unless additional funding was provided to cover these costs.

Mechanisms of impact of the C-reactive protein point-of-care test

Three themes emerged relating to perceptions about how using the CRP POCT might achieve the desired aims: the CRP POCT as an objective sign of illness, the CRP POCT as a patient education tool and the use of the CRP POCT to reinforce the prescriber's decision.

The C-reactive protein point-of-care test as an objective sign of illness

Prescribers reported that the objectivity of the CRP POCT reading was used to support clinical decision-making and reduce decisional uncertainty:

> *I think the clinical decision was, was probably there anyway without needing the CRP test, but obviously there are some instances where, you know, if you're not too sure, then obviously that CRP test could've maybe made that difference as to whether you gave the antibiotics or not.*
>
> *Non-prescriber 2*

Being able to share the reading with patients helped to make the treatment decision-making process more transparent, whereas some other aspects of the clinical examinations were more subjective and/or less visible. One of the clinicians described why they felt that patients liked to have objective tests carried out:

> *Because I think if it's just you face to face and you have no objective evidence, it's just your opinion and they sometimes question that.*
>
> *General practitioner 8*

Primary care staff felt that this enhanced their confidence and reassured both prescribers and patients about their decision with regard to antibiotic treatment:

> *I found writing down 'CRP normal', I found that that was a very powerful of reassuring me and the patient actually, it seemed to place a great deal of, you know, faith on, on blood testing.*
>
> *General practitioner 2*

Patients reported being able to effectively communicate the more visible symptoms of their AECOPD to their clinician. However, the less visible subjective signs of their AECOPD were more difficult to detect and communicate. Patients viewed the CRP POCT as a useful way of objectively measuring the severity of their illness:

> *I thought it [the CRP POCT] was excellent because it was just proving what I already knew if you know what I mean.*
>
> *Participant 5, CRP 20–40 mg/l, prescribed antibiotics*

The C-reactive protein point-of-care test as a patient education tool

Clinicians reported that they used the test result to help explain whether or not they thought that the patient's AECOPD was likely to be caused by a bacterial infection and whether or not antibiotics were likely to be needed. They felt that patients had greater involvement in the consultation through the discussion of the test outcome, and that it provided them with an opportunity to educate patients about antibiotic overuse:

> *It allows you to talk a little bit about antibiotics, you can then, you can, we can then add and refer people to an information sheet about the duration of common symptoms for example.*
>
> *General practitioner 9*

From the patient perspective, there was a reasonable level of understanding of the purpose of the CRP POCT, which they typically discussed in discrete terms [presence/absence of infection (or inflammation) and requirement/no requirement of antibiotics]:

> *Yes, it was to see if I had an infection on my chest and the count of it was I think five, so they decided I didn't have an infection but that the steroids would help me, which they did.*
>
> *Participant 3, CRP < 20 mg/l, no antibiotics*

Although this particular patient recalled her CRP result, most patients showed little evidence of remembering the actual number generated by the test or awareness of how their result compared with that of other patients. In some cases patients were also uncertain about the type of infection the CRP POCT was detecting:

> *They need to confirm, which is what I thought this test and that was doing, that it is, it is a proper viral infection.*
>
> *Participant 6, CRP 20–40 mg/l, prescribed antibiotics*

Use of the C-reactive protein point-of-care test to reinforce prescribers' decisions

Primary care staff felt that the CRP POCT could help make the reasoning behind antibiotic prescribing decisions more transparent and less 'secretive' by providing patients with an objective measure. However, there were very few examples of the CRP POCT facilitating shared decision-making between the patient and the prescriber. The CRP POCT reading was generally used to articulate and justify prescribing decisions, rather than to actively involve patients in these decisions:

> *It gives something to justify to the patient that it's not just your clinical judgement on the signs and things that you have actually done a test and that has, you know, given even more back up that the fact that you confidently don't need antibiotics.*
>
> *General practitioner 6*

From the patient perspective, prescribers were viewed very much as being the decision-makers with regard to antibiotic treatment, and the addition of the CRP POCT appeared to reinforce this power dynamic. Patients were generally very accepting of what the doctor or nurse told them with regard to whether or not they needed antibiotics:

> *I would say my doctors give me sound advice about what to do, because at the end of the day I know they are very busy people and their range of knowledge is quite astounding, and at the end of the day I'm relying on him to give me the correct information to make an educated decision.*
>
> *Participant 7, CRP < 20 mg/l, prescribed antibiotics*

Patients felt that it was right that the doctors made the decisions about antibiotic prescribing:

> *Well I don't think it comes under what the patients want, it's the patient is ill enough to need antibiotics, you know then they should be given, other than that I don't think they should be given, if the patient isn't ill enough for them.*
>
> *Participant 8, CRP < 20 mg/l, no antibiotics*

When patients reported that they felt involved in decisions about antibiotics, they described this in terms of their agreeing with the doctor's decision or because they felt that the doctors had explained their decision to them, rather than being actively involved in the decision-making process per se.

Patients felt that communication was better when clinicians knew them and were familiar with their case, and that a clinician's knowledge of their patient could influence their decisions about antibiotic prescribing:

> *I suppose everyone is an individual, their own fears and state of mind have to be considered, whether they're a hypochondriac or . . . there is a lot to it and I think the doctor would sort of be able to judge his patient if he knew them.*
>
> *Participant 3, CRP < 20 mg/l, no antibiotics*

Primary care staff also felt that their knowledge of the patient and their history was important, and that antibiotics were more likely to be overprescribed when doctors did not know their patients:

> *And that [the CRP POCT] would be even more important in practices where you've got like supermarket medicine going on where you've got hundreds of doctors seeing patients once and never seeing them again where there is not the trust that you get with that sort of relationship.*
>
> *General practitioner 8*

Contextual factors

Attitudes towards antibiotics

There was a high level of awareness among primary care staff of the need to reduce antibiotic prescribing and they acknowledged that there was a general tendency to overprescribe antibiotics. Patient anxiety, a strong patient preference for antibiotics and individual circumstances (e.g. the recent death of a spouse) were cited by primary care staff as possible reasons for still prescribing antibiotics despite a low CRP POCT result, indicating that non-medical factors continue to influence antibiotic prescribing even when an objective measure of the likely severity of infection is available.

Primary care staff had mixed views about the level of awareness of the potential risks of overuse of antibiotics among their patients; some felt that patients had a good awareness and were open to reducing their use, whereas other patients were 'surprised' to learn of the potential downsides of using antibiotics if they were not required. Clinicians frequently discussed the usefulness of the CRP POCT as an educational tool within this social context and talked about a range of wider interventions and resources that aim to alter antibiotic prescribing practices:

> *I think there are really good resources out there for GPs who do want to improve their consulting skills and to having a few ideas about how to open this discussion and to reframe the discussion around antibiotics with patients, um so one of the things that we want to do is get everyone to do those tutorials, sort of just have a few extra tools in their, in their doctor's bag, you know for being able to help that discussion with patients around reducing antibiotic use.*
>
> *General practitioner 9*

Patients' priority was to resolve their symptoms, and there were mixed feelings about when antibiotics should be prescribed. Mostly, patients recognised how valuable antibiotics were when they were needed, but did not want to take them if they were not required:

> *It's not good taking antibiotics just for a minor complaint, you know, you should have it being really bad with your chest before taking antibiotics.*
>
> *Participant 8, CRP < 20 mg/l, no antibiotics*

Some felt that they should take antibiotics for AECOPD regardless (as a precautionary or preventative measure), others felt that people with COPD should take long-term antibiotics in winter and others saw using antibiotics as a last resort. Although the majority of patients reported no adverse effects from previous use of antibiotics, some reported having experienced drawbacks to their use, including allergic reactions, thrush and stomach upsets. A few patients perceived that the antibiotics that they had used had become less effective over time. Some patients reported that they had little or no understanding of antibiotic resistance and the need for antibiotic stewardship, whereas others appreciated the need not to overuse antibiotics:

> *So of course, they [doctors] are a bit concerned about giving me tablets, if I get too used to them and they don't work.*
>
> *Participant 9, CRP < 20 mg/l, no antibiotics*

Patients felt that they had little understanding of how their doctor or nurse made decisions about whether or not antibiotics were required. Most often, patients thought that doctors predominantly based their decision on chest sounds:

> *Well in general they you know listen to my chest and do my blood pressure and that sort of thing, so they usually just do the chest, and decide then whether they think I'm rattling enough to need antibiotics or not.*
>
> *Participant 1, CRP < 20 mg/l, no antibiotics*

Patients discussed antibiotic resistance in terms of their body becoming resistant or 'immune' to the medication, blood becoming resistant or the immune system becoming damaged. A small minority of patients discussed the risk of overuse of antibiotics in terms of the bacteria becoming 'immune' to the medication. However, several patients reported that they were not aware of any disadvantages to antibiotic use:

> *There's no drawbacks at all [to antibiotic use].*
>
> *Participant 10, CRP < 20 mg/l, no antibiotics*

Chronic obstructive pulmonary disease routine care pathway

Clinicians felt that the risk of undertreatment was a driver of antibiotic prescribing for AECOPD:

> *There's so much pressure not to refer patients to hospital, so if you, the view is, if you treat them early, you know, when their symptoms are relatively mild, maybe we'll be able to stop someone going to hospital unnecessarily.*
>
> *General practitioner 9*

Fear of litigation and how the use of the CRP can help provide objective evidence was also discussed:

> *I can only speak for myself, but every patient I see, when I'm writing down, I'm thinking that somebody's going to be suing me as a result of it, which is very sad but it's just the way the world's going, and I think every GP is probably very similar, and I know that if I write down 'CRP less than 5' then anyone taking me to court over that is going to have one hell of a hard time of it to prove that that patient was ill at that point.*
>
> *General practitioner 2*

Patients in some practices were issued with 'rescue packs' containing antibiotics and oral steroids that they could use at home to manage AECOPDs. Patients had mixed views about the use of rescue packs, with some preferring to see a doctor before starting antibiotics and others preferring to start their medication without the need to see a doctor:

> *I'd just rather skip the appointment because you know if you're bad or not don't you? You know what I mean, so if, if I knew I was really ill and I had them in the drawer then I would just take them because I knows what it is now.*
>
> *Participant 11, CRP > 40 mg/l, prescribed antibiotics*

Clinicians also had some ambivalence about rescue packs, expressing the view that these were appropriate only for patients who were able to recognise the symptoms that indicated that antibiotics were required. They felt that there were advantages to rescue packs in terms of encouraging self-management and timely treatment:

> *It [having a rescue pack] improves their confidence, I think in theory it could stop people exacerbating so badly that they end up being admitted to secondary care.*
>
> *General practitioner 5*

Not all practices issued rescue packs to patients, and some did this only when it had been advised by secondary care. The potential for overusing antibiotics and passing on difficult decisions about when to start treatment to the patients were seen as possible disadvantages of using rescue packs:

> *Some patients might find it quite difficult to understand exactly when a leaflet [about use of the rescue pack] is given to them or even when they're explained about the leaflet and when to use the antibiotics, we are leaving the patients to make their own clinical decisions.*
>
> *General practitioner 1*

One clinician suggested that a CRP test that could be easily administered by patients at home could help patients make decisions about when they should start their antibiotics in the future.

Qualitative evaluation summary

Patients and clinicians participating in the PACE trial's qualitative evaluation perceived the CRP POCT as a useful tool to help guide the management of AECOPD in primary care. They described it as providing an objective sign of the severity of illness, increasing confidence and providing reassurance, being a useful tool for patient education, and being helpful in reinforcing the prescriber's decision when communicating with patients. Previous qualitative studies in adults with acute cough have also indicated that CRP POCTs are an acceptable intervention from the perspectives of patients and clinicians, with the main perceived mechanisms of the intervention being reducing clinical uncertainty, increasing prescribing confidence and enhancing communication,[65–67] and our findings were highly consistent with this.

Although CRP POCTs are widely used in a number of European countries for managing LRTIs, they have not yet become routinely used in the NHS.[68] Concerns about funding for the CRP POCT machine and cartridges, and the time needed to use the CRP POCT, were identified as potential barriers to adoption in NHS primary care services. Similar issues have been identified with regard to the routine use of CRP POCTs in the management of LRTIs in NHS primary care services.[68] The primary care staff interviewed in the current study generally felt that the additional time required to complete the test was worth the investment, and felt that the test may help practitioners be less risk-averse when deciding to manage an AECOPD without antibiotics. However, they felt that the costs of the CRP POCT testing equipment and cartridges would be prohibitive under current funding arrangements for NHS primary care services, and this would need to be addressed before it was implemented in routine practice.

There is a lack of evidence for risk stratification based on current clinical assessments in guiding antibiotic prescribing for AECOPD.[69] Our qualitative findings indicated that, in line with this, prescribers felt that the CRP POCT provided useful information in addition to their usual clinical assessment to guide their antibiotic prescribing decisions for AECOPD. They emphasised that the CRP POCT result would not replace other clinical factors in their decision-making but that, rather, it added a piece of objective information for them to consider. Clinicians reported that they would be most likely to use the CRP POCT in routine care in cases when there was clinical uncertainty, which is consistent with the views of clinicians on when the test would be used in the management of LRTIs.[67] In a study[67] of primary care clinicians' views on the potential use of CRP POCTs for LRTIs, clinicians discussed difficulties with interpreting results or being distracted from clinical reasoning as potential disadvantages of the test. The clinicians interviewed in the current study who had used the CRP POCT in consultations did not report experiencing any difficulties in interpreting the test or any negative impact on their clinical judgement.

Contextual factors can influence, and be influenced by, the introduction of an intervention aiming to alter antibiotic consumption for AECOPD, including patient attitudes towards antibiotics and clinician perception of patient preferences,[70,71] and broader issues in relation to the care pathways for COPD, such as continuity of care, patient engagement, resources and communication.[72,73] The current study indicated that, in addition to informing clinicians' decisions about the need for antibiotics, the CRP POCT was used as a tool to educate patients, reinforce clinicians' antibiotic prescribing decisions and facilitate communication. Patients, however, reported that they were not engaging with the decisions being made about antibiotic treatment for their AECOPD. Although they did not report being dissatisfied with this consultation dynamic, their lack of involvement was reflected in their low levels of understanding of the potential disadvantages of using antibiotics and of the purpose of the CRP POCT.

Primary care clinicians' antibiotic prescribing behaviour for acute cough in adults is influenced by their perceptions of patient expectations, but their perceptions do not always match with patient views.[71] Patients report lower levels of satisfaction with their consultation if they have an expectation of receiving antibiotics that is not met.[71] Being able to effectively elicit patient views is, therefore, an important skill for clinicians managing acute cough.[71] A study[33] of the use of CRP POCT to guide antibiotic prescribing for acute respiratory tract infections in primary care indicated that both the CRP POCT and clinician training in communication skills were effective in reducing antibiotic prescribing, but the greatest reduction was seen when the CRP POCT and communication skills training interventions were combined. Patients with acute cough whose clinician had received communication skills training or had used a CRP POCT were satisfied with their consultation even when they had not received an antibiotic.[66] Patients felt positive about the clinician communication skills training, reporting that they felt that their concerns had been understood.[66] Training for prescribers in integrating the CRP POCT into consultations for AECOPD in a patient-centred way may, therefore, enhance its effects.

Patient education is likely to be an important aspect of the successful implementation of the CRP POCT, to ensure that patients understand why the test is needed, have confidence in its use and are sufficiently informed about their treatment options so that they can become more engaged with the decisions that are made about their health care. This is particularly relevant to the population of patients with COPD, as older adults and those from socioeconomically deprived backgrounds are more often affected by this disease,[74] and low health literacy is more prevalent in these demographic groups.[75,76] Ensuring that there is continuity of care and that a consistent approach to antibiotic prescribing for AECOPD is adopted could also increase the quality of communication about the appropriate use of antibiotics in the management of AECOPD and facilitate the implementation of the CRP POCT in routine care.

Conclusions

Patients and clinicians perceived the addition of the CRP POCT to consultations for AECOPD as acceptable and useful. Implementation planning should include consideration of funding arrangements, training for clinicians, patient education, provision of continuity of care and promotion of a consistent approach to prescribing as ways of facilitating implementation and enhancing the effects of the CRP POCT intervention.

Chapter 5 Health economics

Introduction

This chapter presents the methods and results of the economic evaluation conducted alongside the PACE trial. A within-trial health economic analysis was undertaken from a health service perspective (the UK NHS), reflecting the trial follow-up period of 6 months and addressing the secondary trial objective of assessing the costs and cost-effectiveness of using CRP POCT to guide antibiotic prescribing for AECOPD in primary care. Wider costs resulting from patient absences from work were also considered but were reported separately. The health economic evaluation included a cost-effectiveness analysis, a cost–utility analysis (CUA) and a cost–consequences analysis. A trial-based budget impact analysis was undertaken to estimate the likely impact of using CRP POCT in the management of antibiotic prescribing for AECOPD in primary care on NHS budgets.

Methods

Before the analysis commenced, a health economic analysis plan was produced, which was reviewed by the trial team and incorporated in the statistical analysis plan. The health economic team followed this analysis plan during the conduct of the economic evaluation without deviation.

Costs included in the health economic analysis

The health economic analysis considered the following:

- cost of the CRP POCT implementation in primary care (including staff time for training, testing and travel, and costs of CRP POCT kits and consumables)
- costs of medications prescribed (including antibiotics, oral corticosteroids and inhaled medications)
- cost of health-care resource use (primary and secondary care).

As the analyses were undertaken from a NHS perspective, the cost associated with productivity loss due to time off work was assessed but not included in the formal evaluation.

Costs are based on all available cases (for the most complete overview), the MITT population for antibiotic consumption and EQ-5D (for the cost-effectiveness analysis and CUA base cases) and the ITT population (using multiple imputation) for the secondary analysis. All costs are expressed in 2015/16 Great British pounds, inflated and converted appropriately where required.[77] Neither costs nor outcomes were discounted, as the duration of the trial follow-up period did not exceed 1 year.

C-reactive protein point-of-care test costs

Resource use resulting from CRP POCT implementation (including materials, consumables, staff time and training) was estimated through interviews and direct communications with general practice staff involved in the trial, the CRP POCT manufacturer and the trial team, and by using data collected during the trial (e.g. frequency of repeat testing). Unit costs of materials and consumables were obtained directly from the manufacturer and online wholesale catalogues. Staff costs were estimated using published unit costs.[78] Any assumptions were based on clinical expert opinion from the PACE trial team and the impact on the results was tested as part of the sensitivity analysis.

The number of CRP tests performed during the trial was recorded for every participant at baseline and within the first 4 weeks of follow-up.

Cost of medication prescribed for the treatment of acute exacerbations of chronic obstructive pulmonary disease

New prescriptions of medications for treating COPD were recorded routinely during the trial immediately following randomisation and for the 6-month review period. This comprised prescriptions for antibiotics, oral steroids and inhaled medication (including short- and long-acting beta-2 agonists, short- and long-acting muscarinic agonists, inhaled corticosteroids and combination inhalers). Unit costs were taken from the Monthly Index of Medical Specialities[79] and the *British National Formulary*.[80] All medication unit costs used in the costing of the economic evaluation can be found in *Tables 49* and *50* in *Appendix 3*.

Prescriptions were costed individually based on prescribed dose, treatment duration and number of doses per day. For antibiotics and oral steroids, in cases when information on prescribed dose, duration or frequency was missing, the most common prescription of the specific medication was assumed. In cases when no antibiotic or steroid name was reported and when it could not be extrapolated from other information (e.g. dose or duration), the most commonly prescribed antibiotic (500 mg of amoxicillin, 21 tablets) and oral steroid (5 mg of prednisolone, 56 tablets) were assumed. For inhaled medication, it was assumed that, if the medication was increased at the index consultation, a new prescription was issued at the same time. If no information on the type of inhaled medication was available, it was assumed that salbutamol metered dose inhaler (100 mg) was given, using the mean cost of all of its licensed formulations.

The costs of antibiotics, oral steroids and inhaled medications were calculated at the initial consultation, for the 6-month review period and as a total (initial consultation and 6 months combined). It was assumed, for the purpose of the cost-effectiveness analysis, that one-sixth of all medication prescriptions recorded in the 6-month review period would have occurred in the first 4 weeks. This assumption was tested in a sensitivity analysis.

Cost of health-care resource use

Health-care resource use (including primary care consultations, A&E visits, outpatient appointments and inpatient stays) was collected using data from an adapted Client Service Receipt Inventory (CSRI), integrated in the 4-week CRF and 6-month note review, to assess the differences in the profile of health-care use as a result of the intervention compared with control. If one or more items in the health-care consultations part of the CRF (i.e. the CSRI) were completed (values of ≥ 0), the CSRI was assumed to have been fully completed and any missing items were imputed with zeros. If the CRF was marked as 'not done' or was otherwise fully incomplete, data were considered missing and costs were based on all available cases for the base case, using multiple imputation to account for missing data in the secondary analyses.

Costs were assigned using published unit costs.[78,81] Outpatient visits and inpatient stays were costed individually according to the reasons for health-care contact, length of stay and specialty/department visited recorded in the trial CRFs. All unit costs used can be found in *Table 51* in *Appendix 3*. The health-care costs in both trial arms were summated and the mean difference per patient in costs (including 95% CIs) was calculated.

Every patient had one initial index consultation (baseline appointment) during which they were randomised, which was excluded from the 4-week and 6-month follow-up health-care costs but included in the final health economic analysis.

Cost of work lost as a result of acute exacerbations of chronic obstructive pulmonary disease

Participants provided the number of days they had taken off paid employment as a result of AECOPD at the 4-week follow-up time point. Using the Human Capital Approach,[82] days taken off work were costed using a cost of £97.77 per day based on average UK weekly gross earnings for the whole economy during the trial period.[83]

Cost-effectiveness analysis

The cost-effectiveness analysis expressed the incremental cost required to reduce the number of people consuming at least one dose of antibiotics by 1%. The base-case analysis was based on the MITT population for the co-primary outcome of antibiotic consumption at 4 weeks. The total costs at 4 weeks (including costs at the initial consultation) for the MITT population only were considered. The results of the comparative analysis of incremental costs and effects can be summarised in terms of incremental cost-effectiveness ratios (ICERs). An ICER can be represented as:

$$\text{ICER} = \frac{C_1 - C_0}{E_1 - E_0} = \frac{\Delta C}{\Delta E}, \quad (1)$$

where C_1 and E_1 are the costs and effects of the intervention arm and C_0 and E_0 are the costs and effects of the control arm, with ΔC and ΔE the incremental costs and effects of the intervention compared with control.

The ICER is reported to determine the cost-effectiveness of the intervention compared with competing alternatives and to aid decision-making. No established willingness-to-pay threshold for the cost-effectiveness of reducing antibiotic consumption is available. Furthermore, cost-effectiveness is a spectrum rather than a dichotomy, with the maximum threshold increasing depending on the circumstances. The reported ICERs from our analysis are presented to assist the decision-making process and are not an absolute statement on whether or not the intervention can be deemed cost-effective.

Cost–utility analysis

A within-trial CUA was undertaken to assess the incremental costs per quality-adjusted life-year (QALY) gained as a result of using CRP POCT compared with control at 6 months. Individual-level utility scores were obtained at each assessment point using the EQ-5D-5L questionnaire mapped back to the UK EQ-5D-3L valuation set, as currently recommended,[84] and summated for the CRP POCT and control arms. During the internal pilot, the EQ-5D-3L version of the questionnaire was used and health states were transformed using UK EQ-5D-3L valuation sets. QALYs for each patient were calculated based on the utility scores at baseline and 6 months using the area under the curve approach and linear interpolation. The total costs at 6 months (including baseline) for the EQ-5D MITT population were used to calculate the incremental cost per QALY gained. The EQ-5D MITT population comprised all patients who had a complete baseline questionnaire and any one complete follow-up questionnaire.

Quality-adjusted life-years incorporate quantity of life (additional life-years) and quality of life in one measure. Thus, by dividing the difference in costs by the difference in QALYs, the cost per QALY can be calculated for each comparison. Generally, NICE considers an intervention cost-effective if one of the following applies:

- The intervention is less costly and more clinically effective than all other relevant alternatives. In this case, no ICER is calculated as the strategy in question dominates the alternatives.
- The intervention has an ICER of < £20,000 per QALY compared with the next best alternative. This means that an investment of up to £20,000 to achieve an additional QALY is considered cost-effective.

The ICER resulting from the CUA was compared with the willingness-to-pay threshold of £20,000 per QALY gained as standardised by NICE. No conditions for non-inferiority were applied in this analysis. The results are reported as ICERs showing the extra cost of producing one extra QALY or the extra savings achieved by sacrificing one additional QALY.

Sensitivity analyses

Sensitivity analyses were undertaken to test the robustness of the results of both cost-effectiveness analysis and CUA, considering the uncertainty in input parameters, such as costs and outcomes, and in different scenarios. Deterministic, univariate sensitivity analyses changed test, medication and health-care costs and

outcomes individually within plausible ranges. Scenario analyses tested different assumptions and recalculated the ICER using COPD-related costs only. Furthermore, a probabilistic sensitivity analysis used non-parametric bootstrapping to address joint parameter uncertainty and assess the impact on the ICER during 1000 simulations that were undertaken using random sampling of the distributions of costs and outcomes, with results presented on cost-effectiveness planes and as cost-effectiveness acceptability curves. The cost-effectiveness plane is a scatterplot of the point estimates obtained as a result of the 1000 simulations depicted in four quadrants, representing the probability of the intervention being more or less costly and more or less effective than the control. A cost-effectiveness acceptability curve is a curve that describes the probability of the intervention being cost-effective at different willingness-to-pay thresholds based on the probabilistic sensitivity analysis.

We also undertook a secondary analysis in the ITT population using multiple imputation to account for missing data. The problems concerning missing data are particularly relevant to health economic analysis, as the main outcomes are cumulative measures collected during the trial. Missing items relating to health-care service usage may underestimate the total costs, and missing outcome data may be correlated with effects, as those individuals without information may be systematically different from those for whom all information is observed.[85] As such, using only complete-case assessments and available cases analysis could result in meaningful data being excluded.[85] We therefore adopted a multiple imputation approach as the appropriate technique to provide a comprehensive investigation of the impact of missing data on the estimations of cost-effectiveness.[86] Multiple imputation was performed using chained equations and predictive mean matching on all variables except categorical (yes/no) parameters, where multiple imputation using logistic regression was deemed appropriate given values of 0 and 1 only. Predictive mean matching for continuous variables was preferred to other methods as imputed values are taken from the set of observed values, avoiding any values outside plausible ranges (e.g. utility values of > 1 and costs of < £0). A total of 20 imputations were added. The results were combined using Rubin's rules.[87]

Cost–consequences analysis

A cost–consequences analysis presents all relevant primary and secondary outcomes alongside the costs in tabular form (without combining them into ICERs) to leave decision-makers the option to form their own view of relative importance.

Budget impact analysis

A trial-based budget impact analysis was undertaken and extrapolated to the UK population to estimate the likely impact of using CRP POCT on NHS budgets through implementation costs and changes in health-care usage. The budget impact analysis was informed by trial data supplemented by the best available published evidence when required and conducted according to recommended good practice.[88]

A simple budget impact model was constructed in Microsoft Excel® 2010 (Microsoft Corporation, Redmond, WA, USA). The number of eligible patients was calculated using prevalence and yearly incidence figures and accounting for age-specific and COPD mortality. Prevalence, incidence and mortality data for COPD in the UK were obtained from published sources[89] and age-specific general population mortality was derived from statistics available on deaths in England and Wales in 2016.[90] It is estimated that, since 2012,[89] the yearly incidence of COPD in the UK has been steady, at around 115,000 new diagnoses, and the budget impact analysis, therefore, assumes the incidence to be constant over the first 5 years after CRP testing is introduced in primary care. It also assumes that all diagnosed patients experience one AECOPD per year and are eligible for CRP testing. The expected uptake rate is assumed to be 10% in year 1, rising to 50% depending on the installation of the required analysers in general practices. The costs of testing and subsequent health-care resource use were taken from the trial costings.

Sensitivity analyses were undertaken to estimate the range of a potential budget impact considering parameter uncertainty within plausible ranges.

Results

Four participants were excluded from all analyses (three withdrew consent to use their data and one was randomised in error).

C-reactive protein point-of-care test costs

The total cost of a CRP POCT was estimated to be £11.31 per test (*Table 19*). This cost comprises £5.40 for materials and consumables (including quality control tests), £0.13 for capital expenditure, £0.10 for staff training and £5.38 for staff required for sample processing, testing and reporting. During the trial baseline CRP testing, 10 out of 333 tests were invalid or resulted in an error message, requiring repeat testing. Therefore, a cost of £0.29 was added to each test to account for material and staff costs required for repeat testing.

TABLE 19 Cost components and total testing cost of CRP POCT in primary care

Cost component	List price (£)	Resource use	Cost per test (£)	Notes
Material costs				
Alere Afinion CRP test cartridge[a]	58.00	1	3.87	No discounts given, 15 cartridges per pack
Alcohol wipe[b]	2.00	1	0.02	100 wipes per pack
Prick needle[c]	7.50	1	0.08	100 lancets per pack
Gauze pads/swabs[d]	15.30	1	0.06	250 pads per pack
Gloves[e]	9.19	2	0.18	100 per pack
Quality control testing kits[a]	36.00	0.13	1.20	Four per pack. One high level and one low level control required per 15 tests
Repeat samples because of invalid results[f]	58.00	0.03	0.13	10/333 tests at baseline gave an error (3.0%)
Capital costs				
Alere Afinion AS100 Analyzer[a]	1200.00	0.00011	0.13	7-year life span (five samples per day assumed, 260 working days per year) = 9100 samples
Maintenance contract[a]		None	0.00	No maintenance required
Set-up and training				
Initial set-up, calibration and configuration[a]			0.00	Done by supplier before training
Travel and trainer cost			0.00	Done at GP surgery, included in purchase price
GP opportunity cost[g]	134.00/hour	45 minutes	100.50	GMS activity including qualifications and excluding direct care staff
Nurse opportunity cost[g]	43.00/hour	45 minutes	32.25	Including qualifications
Testing				
Analyser switch-on and self-test[a,g]	43.00/hour	1 minute	0.14	Nurse assumed, 1 minute needed, five tests per day assumed
Sample processing (including taking sample, labelling, preparation and test start) by GP[g]	199.00/hour	1.15 minutes	3.81	Patient contact excluding direct care staff, 1 minute and 9 seconds average processing time,[a] assumed 70% of cases

continued

TABLE 19 Cost components and total testing cost of CRP POCT in primary care (*continued*)

Cost component	List price (£)	Resource use	Cost per test (£)	Notes
Sample processing (including taking sample, labelling, preparation and test start) by nurse	43.00/hour	1.15 minutes	0.82	Including qualifications, 1 minute and 9 seconds average processing time,[a] assumed 30% of cases
Results check and reporting (GP)	199.00/hour	0.7 minutes	2.32	
Dealing with testing errors and retesting	199.00/hour	0.03	0.16	10/333 tests at baseline required retesting
Total test cost			11.31	

GP, general practitioner.
a Source: Alere Inc. (Adam Martin, 21 July 2017, personal communication).
b Source: Medisupplies.[91]
c Source: Amazon.[92]
d Source: Medisupplies.[93]
e Source: Scientific Laboratory Supplies.[94]
f Source: PACE trial.
g Source: Personal Social Services Research Unit, 2016.[78]

Three participants in the control arm received CRP tests at baseline in error and eight participants in the CRP POCT arm did not have test results as a result of machine errors. Four participants in the control arm self-reported a CRP test at baseline, with no other records to clarify.

Considering all available cases ($n = 649$), the total cost of CRP testing at baseline in the CRP POCT arm ($n = 325$) was £3697.54, with a mean of £11.38 per participant (SD £1.25 per participant). Assuming that the four unresolved patients did not receive a CRP test, the total cost in the control arm ($n = 324$) was £33.92, with a mean of £0.10 per patient (SD £1.09 per patient), increasing to £79.16 (mean £0.24 per patient, SD £1.64 per patient) if it is assumed that the four unresolved cases did receive a CRP test.

In the first 4 weeks after randomisation, 18 patients in the CRP POCT arm received 20 CRP tests. This increases the total cost of CRP testing at the 4-week follow-up point (including baseline) to £3923.69 in the CRP POCT arm (mean cost per patient £12.08, SD £3.23).

Cost of medication prescribed for treatment of acute exacerbations of chronic obstructive pulmonary disease

A breakdown summary of the mean costs for all recorded medication prescriptions is shown in *Table 20*. The total medication costs for the CRP POCT and control arms are presented in *Appendix 3*, *Table 52*.

Antibiotics

Considering all available cases ($n = 649$), 155 patients in the CRP POCT arm (47.7%) were prescribed antibiotics at their baseline general practitioner (GP) consultation following CRP testing, compared with 225 patients in the control arm (69.4%). This resulted in a cost saving of £0.28 (95% CI –£0.39 to –£0.17) per patient at baseline (see *Table 20*). The most commonly prescribed antibiotic was amoxicillin (59.5%), followed by doxycycline (24.0%), clarithromycin (12.8%), co-amoxiclav (1.9%), erythromycin (1.3%) and cefalexin (0.5%).

In the 6-month review period ($n = 606$), 173 patients in the CRP POCT arm (56.9% of 304 patients) were issued 403 antibiotic prescriptions, and 191 people in the control arm (63.2% of 302 patients) had received 404 antibiotic prescriptions. Of these, 80.6% were attributed to COPD and lung conditions (including rescue packs) in the CRP POCT arm and 79.7% were attributed to COPD and lung conditions (including rescue packs) in the control arm. Other most common indications for which antibiotics were issued were urinary tract infections, skin infections, wound infections and infected ulcers. In total, 12.8%

TABLE 20 Cost of antibiotics, oral steroids, inhaled medications and all medications at baseline and 6-month follow-up

Medication	Trial arm, mean (SD)		Difference (95% CI)	*p*-value
	CRP POCT ($n = 325$)	Usual care ($n = 324$)		
Antibiotics				
Cost at index consultation (£), per patient	0.63 (0.69)	0.91 (0.72)	–0.28 (–0.39 to –0.17)	0.029
Cost at 6-month review (£), per patient	2.20 (4.69)	2.05 (2.78)	0.15 (–0.46 to 0.77)	0.251
Oral steroids				
Cost at index consultation (£), per patient	0.75 (0.77)	0.74 (0.73)	0.02 (–0.10 to 0.13)	0.862
Cost at 6-month review (£), per patient	1.10 (1.92)	1.26 (2.88)	–0.16 (–0.55 to 0.23)	0.491
Inhaled medications				
Cost at index consultation (£), per patient	3.14 (8.82)	3.10 (8.41)	0.05 (–1.33 to 1.42)	0.889
Cost at 6-month review (£), per patient	10.05 (18.65)	7.74 (16.20)	2.30 (–0.49 to 5.09)	0.109
Total medication cost				
Cost at index consultation (£), per patient	4.51 (8.74)	4.70 (8.39)	–0.21 (–1.57 to 1.16)	0.905
Cost at 6-month review (£), per patient	13.35 (19.55)	11.05 (17.00)	2.30 (–0.62 to 5.22)	0.341

fewer patients received any antibiotic prescriptions in the 6 months following the baseline GP consultation in the CRP POCT arm, the patients who were issued prescriptions had, on average, 0.21 prescriptions more than patients in the control arm (2.33 vs. 2.12). Furthermore, the prescriptions issued were for more expensive antibiotic formulations (mean of £1.66 per prescription, compared with £1.53 in the control arm), resulting in a £0.15 increase in cost of antibiotics per patient in the CRP POCT arm ($p = 0.251$).

Overall, when initial consultation and 6-month review period prescriptions were combined, the mean cost of antibiotics in the CRP POCT arm was reduced by £0.13 (95% CI –£0.72 to £0.46) per patient ($p = 0.135$).

Oral corticosteroids

All oral corticosteroids prescribed at baseline were prednisolone formulations. In the CRP POCT arm, 178 patients (54.9% of 324) received oral steroids compared with 179 patients (55.6% of 322) in the control arm. Patients who were issued prescriptions for oral steroids received, on average, 1.00 prescription in the control arm and 1.02 prescriptions in the CRP POCT arm, resulting in a marginal cost increase of £0.02 per patient in the CRP POCT group (see *Table 20*).

During the 6-month follow-up period, 130 patients in the CRP POCT arm (42.8% of 304) received 279 prescriptions for oral steroids, of which 91.4% were issued for COPD and related respiratory disease. In the control arm, 146 patients (48.3% of 302) were issued 271 steroid prescriptions, of which 95.9% were related to COPD and respiratory conditions. Although 5.5% fewer people received any oral steroid prescriptions in the CRP POCT arm, they were issued 0.29 more prescriptions for oral steroids per patient (2.15 vs. 1.86 in the control arm). However, the average cost of oral steroid prescriptions per patient was lower in the CRP POCT arm (£1.20 vs. £1.40 in the control arm), partially driven by the higher cost of dexamethasone for one patient in the control arm. The cost of oral steroids during the 6-month review period was, therefore, £0.16 per patient (95% CI –£0.55 to £0.23; $p = 0.491$) lower in the CRP POCT arm.

Overall, when baseline and 6-month review period prescriptions were combined, oral steroid cost was reduced by £0.12 (95% CI –£0.52 to £0.28; $p = 0.482$) per patient receiving the intervention.

Inhaled medications

In the CRP POCT arm, 71 patients (21.9% of 324) were prescribed new inhaled medications or had their existing prescription increased at baseline, resulting in 87 prescriptions (1.23 per patient receiving any inhaled medication prescriptions). This was similar to the 73 patients (22.7% of 321) in the control arm who were issued 86 prescriptions for inhaled medications (1.18 per patient receiving any inhaled medication prescriptions). The marginally higher cost of £0.05 per patient (see *Table 20*) reflects the cost of one additional prescription in the CRP POCT arm.

During the 6-month follow-up period, 93 CRP POCT arm patients (30.6% of 304) received 124 prescriptions for inhaled medications (1.33 per patient receiving any prescriptions). This was 5.4% more than in the control arm, in which 76 patients (25.2% of 302) were issued 94 inhaler prescriptions (1.24 per patient receiving a prescription). Owing to the increased use of inhalers in the CRP POCT arm and the higher acquisition cost (on average approximately £22 per prescription), the total cost of inhaled medications during the 6-month review period was £2.30 higher per patient (95% CI –£0.49 to £5.09 per patient).

Overall, when baseline and 6-month review period prescriptions were combined, inhaler cost was £2.21 (95% CI –£0.75 to £5.18; $p = 0.228$) per patient higher in the CRP POCT arm than in the control arm.

Cost of health-care resource use

The costs reported represent the mean cost per patient. The total health-care costs for CRP POCT and control arms are summarised in *Appendix 3*, *Tables 53* and *54*.

Primary care costs

In the first 4 weeks following randomisation, 27.6% of people in the CRP POCT arm (76/275 available cases) saw their GP at the surgery for any reason an average of 1.45 times. This represents a difference of 7.7% compared with the control arm, in which 35.4% of patients (99/280 available cases) had an average of 1.42 GP visits at their surgery, and results in a cost difference for GP visits at the surgery in the CRP POCT arm of –£3.73 per person (95% CI –£8.38 to –£0.92 per person; $p = 0.07$).

Patients in the CRP POCT arm accrued slightly higher total costs for nurse consultations and other health-care contacts (NHS Direct) than those in the control arm. However, this was more than offset by savings from fewer GP contacts, with an overall cost difference of –£4.58 (95% CI –£13.55 to £4.39; $p = 0.132$) per patient for all primary care use in the CRP POCT arm, which was mainly driven by savings in GP visits at the surgery and GP telephone consultations (*Table 21*).

During the 6-month review period (which includes the first 4 weeks but excludes the baseline), 259 people saw their GP at the surgery for any reason in both arms (85.7% of available cases in the control arm and 85.2% of available cases in the CRP POCT arm). Patients in the CRP POCT arm saw their GP for any condition on average 3.8 times. This was slightly more frequently than the 3.7 times in the control arm, resulting in a cost increase of £3.21 per patient (see *Table 21*). Considering all primary care contacts, costs for patients in the CRP POCT arm were £5.16 (95% CI –£18.14 to £28.47; $p = 0.882$) per person more than for control arm patients.

However, when analysing primary care contacts related to COPD only (*Table 22*), fewer patients had GP home visits, nurse home visits and GP telephone consultations in the CRP POCT arm than in the control arm. Furthermore, GP surgery consultations for COPD were 2.7% less frequent (58.6% vs. 61.3%), with slightly fewer visits per patient (2.18 visits in CRP POCT arm compared with 2.27 visits in the control arm), resulting in an overall difference in primary care cost due to COPD in the CRP POCT arm of £6.35 per patient (95% CI –£18.98 to £6.27; $p = 0.515$).

TABLE 21 Cost of primary care resources used in the 4-week follow-up and 6-month review periods

Health-care resource	Trial arm: CRP POCT ($n = 275$)	Trial arm: Usual care ($n = 280$)	Difference (95% CI)	*p*-value
Primary care: cost per patient in 4-week follow-up period				
GP visits at the surgery (£) (SD)	14.40 (26.64)	18.13 (29.08)	–3.73 (–8.38 to –0.92)	0.070
Nurse visits at the surgery (£) (SD)	2.79 (7.43)	2.47 (5.55)	0.32 (–0.77 to 1.41)	0.950
GP visits at home (£) (SD)	1.24 (10.20)	1.52 (13.38)	–0.28 (–2.27 to 1.70)	0.984
Nurse visits at home (£) (SD)	0.09 (1.43)	0.17 (2.01)	–0.08 (–0.37 to 0.21)	0.574
GP telephone consultations (£) (SD)	2.98 (10.55)	4.01 (14.19)	–1.02 (–3.11 to 1.07)	0.579
Nurse telephone consultations (£) (SD)	0.22 (1.20)	0.19 (1.26)	0.03 (–0.18 to 0.23)	0.592
Other health-care contacts (£) (SD)	1.86 (26.47)	1.67 (26.20)	0.19 (–4.20 to 4.58)	0.303
Total cost of primary care use (£) per patient (SD)	23.57 (52.34)	28.16 (55.16)	–4.58 (–13.55 to 4.39)	0.132
Primary care: cost per patient in 6-month review period				
GP visits at the surgery (£), (SD)	117.59 (102.44)	114.32 (93.48)	3.27 (–12.37 to 18.92)	0.969
Nurse visits at the surgery (£), (SD)	18.04 (24.84)	16.72 (29.44)	1.32 (–3.02 to 5.67)	0.120
GP visits at home (£), (SD)	6.99 (42.83)	9.57 (40.45)	–2.58 (–9.23 to 4.07)	0.364
Nurse visits at home (£), (SD)	1.80 (20.51)	1.42 (13.76)	0.38 (–2.41 to 3.17)	0.521
GP telephone consultations (£), (SD)	27.90 (51.32)	25.28 (46.39)	2.62 (–5.18 to 10.43)	0.540
Nurse telephone consultations (£), (SD)	1.39 (3.66)	1.31 (4.16)	0.08 (–0.55 to 0.70)	0.818
Other health-care contacts (£), (SD)	0.28 (1.78)	0.22 (1.80)	0.06 (–0.22 to 0.35)	0.413
Total cost of primary care use (£) per patient (SD)	174.00 (153.48)	168.83 (138.20)	5.16 (–18.14 to 28.47)	0.882

TABLE 22 Cost of primary care resources used in the 6-month review period related to COPD

Health-care resource	Trial arm (£), mean (SD): CRP POCT ($n = 304$)	Trial arm (£), mean (SD): Usual care ($n = 302$)	Difference (£) (95% CI)	*p*-value
Primary care related to COPD: cost per patient				
GP visits at the surgery	45.95 (55.06)	50.07 (59.78)	–4.12 (–13.29 to 5.05)	0.489
Nurse visits at the surgery	7.31 (10.44)	6.67 (11.83)	0.64 (–1.14 to 2.42)	0.115
GP visits at home	3.08 (18.66)	4.50 (22.53)	–1.43 (–4.73 to 1.87)	0.376
Nurse visits at home	0.00 (0.00)	1.10 (13.12)	–1.10 (–2.41 to 0.37)	0.044
GP telephone consultations	10.89 (25.96)	11.23 (28.26)	–0.34 (–4.67 to 3.99)	0.735
Nurse telephone consultations	0.82 (2.63)	0.76 (2.79)	0.06 (–0.37 to 0.49)	0.441
Other health-care contacts	0.09 (0.94)	0.16 (1.63)	–0.06 (–0.28 to 0.15)	0.987
Total cost of primary care use per patient	68.13 (72.34)	74.49 (85.37)	–6.35 (–18.98 to 6.27)	0.515

Secondary care costs

Secondary care resource use is summarised in *Table 23*. A summary of secondary care costs can be found in *Table 24*.

In the first 4 weeks of follow-up, the secondary care costs were £13.74 (95% CI –£45.87 to £73.35; $p = 0.842$) per person higher in the CRP POCT arm, mainly as a result of an increased number of inpatient stays.

In the 6-month review period, the total secondary care cost was £112.40 (95% CI –£106.67 to £331.46; $p = 0.523$) per person higher in the CRP POCT arm (see *Table 24*), mainly caused by, on average, 3.03 days (95% CI –0.08 to 6.14 days; $p = 0.342$) longer inpatient hospital stays in the CRP POCT arm (7.78 days vs. 4.75 days in the control arm). This was attributed to a higher number of stays exceeding 10 days in the CRP POCT arm (eight stays of > 10 days, of which three were COPD/respiratory related) than in the control arm (three stays of > 10 days, all of which were COPD/respiratory related), including two patients who experienced prolonged inpatient stays (> 20 days) as a consequence of a stroke and a fall.

Considering only COPD-related causes, the total secondary care cost was marginally lower in the CRP POCT arm despite the mean length of hospital stay being 1.68 days longer (95% CI –1.92 to 5.28 days; $p = 0.617$) than in the control arm (6.42 days vs. 4.74 days).

Total costs at 4 weeks and 6 months

The total costs from a NHS perspective at the 4-week follow-up time point (including baseline costs) were £143.93 (SD £348.96) and £126.34 (SD £329.37) in the CRP POCT and control arms, respectively, resulting in a difference of £17.59 per patient (95% CI –£34.80 to £69.98 per patient; $p = 0.408$) with higher costs in the CRP POCT arm. This was a result of the CRP testing costs and higher inpatient costs in the CRP POCT arm that could not be offset by savings in primary care (*Figure 7*).

In the 6-month review period (including baseline), the mean cost per patient for any condition in the CRP POCT arm was £732.31 (SD £1660.08) and £606.04 (SD £1009.32) in the control arm, representing a cost increase of £126.26 per patient (95% CI –£85.92 to £338.45 per patient; $p = 0.680$). This was mainly driven by higher inpatient costs, slightly increased primary care costs and the cost of CRP testing (*Figure 8*).

TABLE 23 Secondary care resources used per patient in the trial follow-up period

	Trial arm, *n* (mean, SD)	
Health-care resource	CRP POCT (*n* = 275)	Usual care (*n* = 280)
Secondary care resource use in the 4-week follow-up period		
A&E visits	13 (0.05, 0.21)	9 (0.03, 0.18)
Outpatient visits	35 (0.11, 0.41)	42 (0.13, 0.37)
Inpatient stays	7 (0.02, 0.15)	4 (0.01, 0.11)
Secondary care resource use in the 6-month review period	*n* = 305	*n* = 302
A&E visits	82 (0.25, 0.69)	76 (0.23, 0.61)
Outpatient visits	380 (1.17, 1.55)	393 (1.21, 1.60)
Inpatient stays	35 (0.11, 0.44)	34 (0.10, 0.38)
Secondary care resource use in the 6-month review period related to COPD only		
Total A&E visits related to COPD, *n* (% of all visits)	35 (42.7)	33 (43.4)
Total outpatient visits related to COPD, *n* (% of all visits)	8 (21.1)	11 (26.2)
Total inpatient stays related to COPD, *n* (% of all visits)	17 (48.6)	21 (61.8)

TABLE 24 Cost of secondary care resources used per patient in the trial follow-up period

Health-care resource	Trial arm (£), mean (SD)		Difference (£) (95% CI)	*p*-value
	CRP POCT (*n* = 275)	Usual care (*n* = 280)		
Secondary care cost per patient during the 4-week follow-up period				
A&E visits	6.92 (31.44)	5.12 (29.27)	1.80 (–3.26 to 6.86)	0.366
Outpatient visits	14.45 (53.23)	20.98 (76.26)	–6.53 (–17.50 to 4.44)	0.138
Inpatient stays	52.32 (343.41)	31.44 (310.45)	20.88 (–33.68 to 75.44)	0.346
Other secondary care use	8.05 (42.51)	10.51 (62.00)	–2.46 (–11.34 to 6.41)	0.246
Total cost of secondary care use per patient	81.80 (369.35)	68.05 (345.38)	13.74 (–45.87 to 73.35)	0.842
Secondary care cost per patient in the 6-month review period for any reason				
	n = 305	*n* = 302		
A&E visits	37.03 (98.02)	34.66 (86.56)	2.37 (–12.38 to 17.12)	0.713
Outpatient visits	151.99 (208.14)	157.51 (205.98)	–5.53 (–38.54 to 27.49)	0.782
Inpatient stays	347.69 (1581.94)	232.91 (983.98)	115.55 (–90.35 to 322.46)	0.802
Total cost of secondary care use per patient	536.71 (1673.02)	424.32 (983.98)	112.40 (–106.67 to 331.46)	0.523
Secondary care cost per patient in the 6-month review period for COPD-related reasons only				
A&E visits	16.26 (61.07)	14.60 (55.35)	1.66 (–7.63 to 10.95)	0.903
Outpatient visits	24.06 (77.74)	36.84 (105.53)	–12.79 (–27.55 to 1.98)	0.115
Inpatient stays	134.16 (855.00)	123.57 (625.23)	10.59 (–108.90 to 130.09)	0.568
Total cost of secondary care use per patient	174.48 (911.54)	175.01 (669.57)	–0.53 (–128.13 to 127.07)	0.271

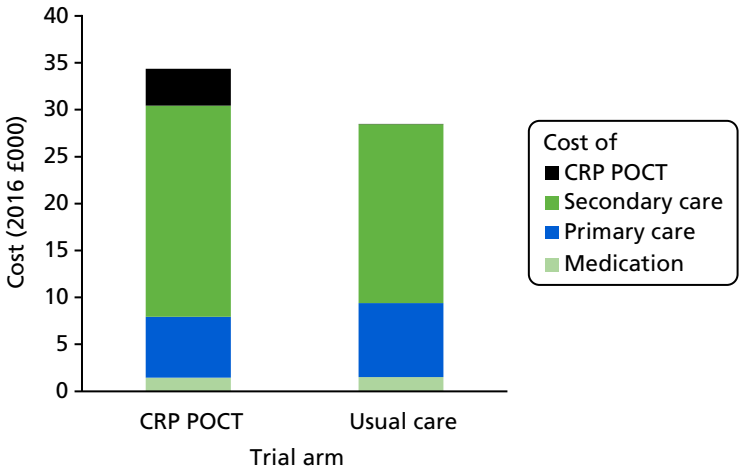

FIGURE 7 Costs accrued in the first 4 weeks of follow-up (including baseline but excluding medication costs between baseline and 4 weeks because of a lack of data).

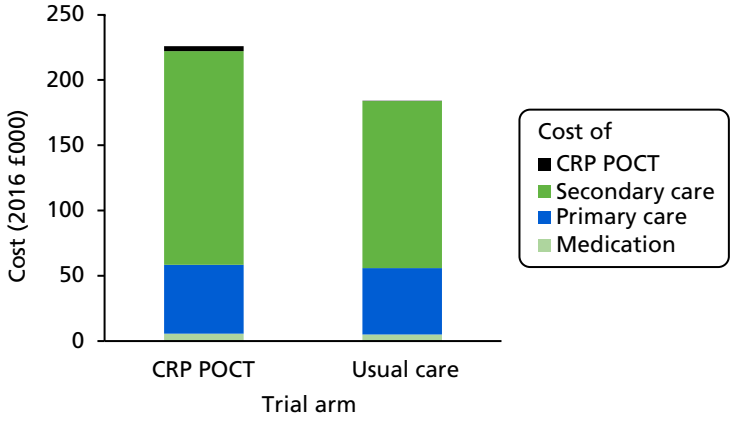

FIGURE 8 Costs accrued for any condition in the 6-month review period (including baseline costs).

However, considering only health-care resource use related to COPD, the total cost was similar in both arms (*Figure 9*), with £294.14 per patient in the CRP POCT arm and £287.33 per patient in the control arm, resulting in a cost difference of £6.81 per patient (95% CI –£116.49 to £130.11 per patient; $p = 0.986$).

Cost of work lost due to acute exacerbations of chronic obstructive pulmonary disease

In the CRP POCT arm, 274 patients provided information on whether or not they took time off paid employment because of COPD. At the 4-week follow-up point, 30.7% were in paid employment at the time of reporting. Of these, 19.0% reported sickness leave and took an average of 4.3 days off work because of illness (a total of 69 days off work). This amounted to a cost of £421.62 per person.

By comparison, 280 people provided information in the control arm, of whom 27.5% were in paid employment at the time of reporting. Of these, 19.5% took a total of 143 days off work, which equals 9.5 days per person. This results in a cost of £932.04 per person in work lost.

Cost-effectiveness analysis

The mean cost for the MITT population ($n = 537$) at the 4-week follow-up point (including baseline) was £161.77 (SD £385.58) in the CRP POCT arm ($n = 274$) and £116.68 (SD £223.46) in the control arm ($n = 263$). This represents an incremental cost of £45.09 per person (95% CI £8.07 to £98.26 per person; $p = 0.020$) in the CRP POCT arm. Considering that 77.4% of patients in the control arm consumed antibiotics compared with 57.0% of patients in the CRP POCT arm (see *Chapter 3*), the mean ICER is £222 (95% CI –£42.00 to £518.14) per 1% absolute reduction in antibiotic consumption. For the base case, the four unresolved control patients who reported a CRP POCT test are assumed to not have received a test.

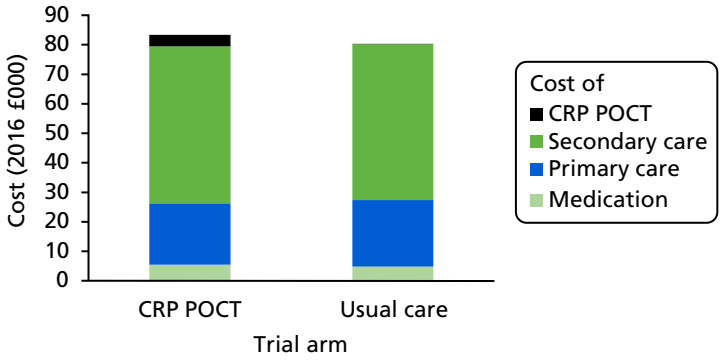

FIGURE 9 Total costs during study period for CRP POCT and control arm, respectively. Costs associated with COPD and other respiratory conditions only (including baseline costs).

Sensitivity analyses

The results of the sensitivity analyses can be found in *Table 25*. In all analyses, ICERs ranged between £120 and £234 per 1% reduction in antibiotic consumption. ICERs were generally robust but were most affected by changes in health-care costs and the exclusion of health-care costs not related to COPD.

Probabilistic sensitivity analysis gave a point estimate of the ICER of £196, with the majority of results more costly but also more effective in the CRP POCT arm, with some iterations where CRP POCT dominates control (i.e. less costly and more effective; *Figures 10* and *11*).

TABLE 25 Results of the deterministic sensitivity analyses and scenario analyses on the primary base-case cost-effectiveness analysis results

Parameter	Change(s)	ICER (£)
Deterministic one-way sensitivity analysis		
CRP POCT costs	Remove GP training cost. Assume machine used for other tests in routine practice. Assume testing carried out predominantly by nurses, change cost ±20%	211 to 234
Medication costs	Change costs ±20%	222 (marginal change)
Health-care costs	Change costs ±20%	190 to 255
Antibiotic consumption	Change antibiotic consumption by ±20%	212 to 319
Scenario analysis		
CRP POCT costs	Four unresolved control cases assumed to have received CRP test at baseline	222
Medication cost in 4-week follow-up period	No medication cost considered. Medication cost increased to one-third of 6-month review costs	220 to 224
Health-care costs	COPD-related health-care costs only considered	120

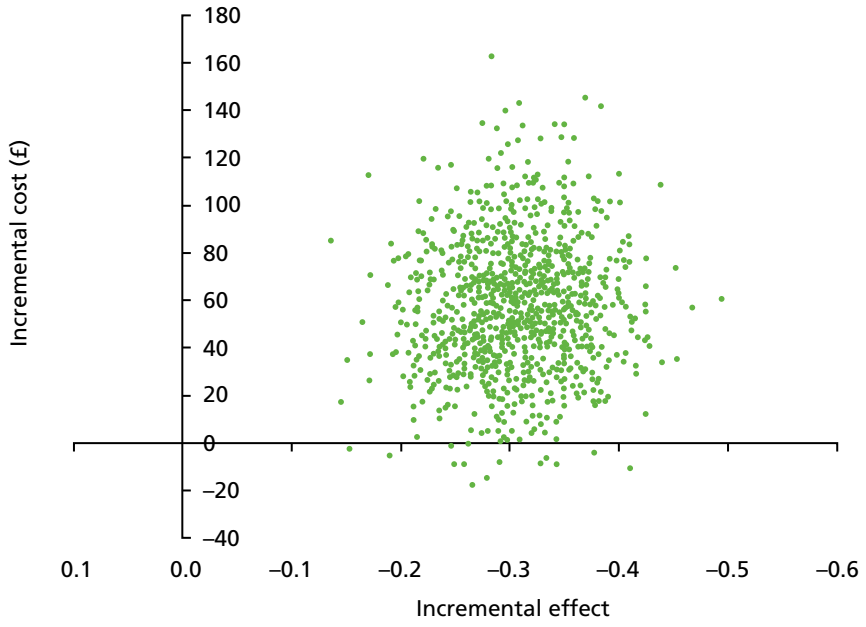

FIGURE 10 Cost-effectiveness plane (MITT analysis) for the base case (incremental cost per percentage reduction in antibiotic consumption).

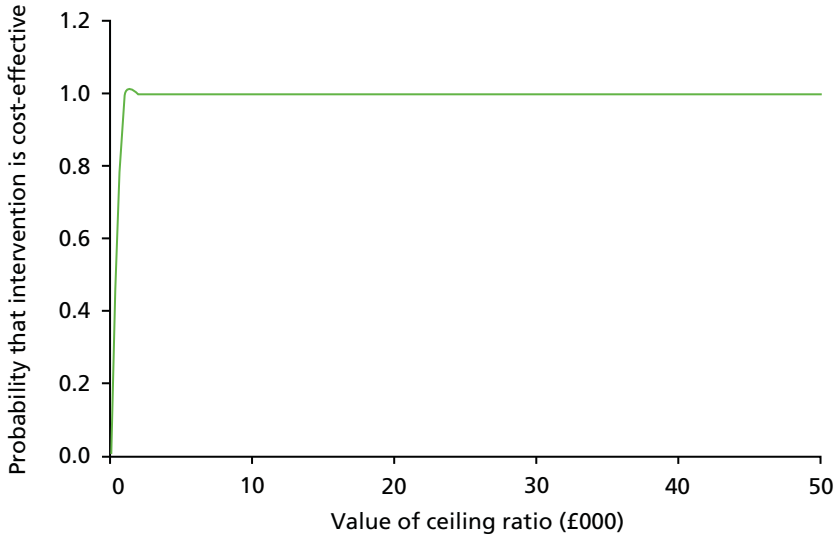

FIGURE 11 Cost-effectiveness acceptability curve for base-case cost-effectiveness analysis.

Cost–utility analysis

The total cost at 6 months (including baseline) for the EQ-5D MITT population was £759.35 (SD £1712) per person in the CRP POCT arm ($n = 301$) and £629.72 (SD £1036) per person in the control arm ($n = 301$). The number of QALYs gained over the 6-month review period was small in both arms, with a mean of 0.2915 (SD 0.1240) in the control arm and 0.3000 (SD 0.1275) in the CRP POCT arm, giving a marginal QALY increase of 0.0085 (95% CI –0.0117 to 0.0286; $p = 0.760$). This results in an ICER of £15,251 (95% CI £2959 to £22,813) per QALY gained.

Sensitivity analyses

Results remained reasonably robust during deterministic sensitivity analyses when subjected to changes in the cost inputs with ICERs between £12,519 and £19,063 and health-care cost as the main cost driver. Owing to the small between-arm differences in QALY gain, results were more sensitive to changes in this variable (*Table 26*).

TABLE 26 Results of the deterministic sensitivity analyses and scenario analyses on the base-case CUA results

Parameter	Change(s)	ICER (£)
Deterministic one-way sensitivity analysis		
CRP POCT costs	Remove GP training cost. Assume machine used for other tests in routine practice. Assume testing carried out predominantly by nurses, change cost ±20%	14,980 to 15,521
Medication costs	Change costs ±20%	15,195 to 15,304
Health-care costs	Change costs ±20%	12,519 to 17,980
QALY gain	Change QALY gain ±20%	12,835 to 19,063
Scenario analysis		
QALY gain	All patients completing EQ-5D-3L excluded	8444[a]
CRP POCT costs	Four unresolved control cases assumed to have received CRP test at baseline	15,238
Health-care costs	COPD-related health-care costs only considered	1054

a Excluding all internal pilot patients reduced costs in the intervention arm, as one excluded patient had a long-term hospital stay (unrelated to COPD) associated with high cost.

Scenario analysis showed that the ICER would be reduced to £1054 per QALY gained if COPD-related health-care costs only were included in the analysis, with a probability of the intervention being cost-effective at the £20,000 threshold of 72%.

In the probabilistic sensitivity analysis most results found CRP POCT to be more costly but also more effective. However, results are distributed across all quadrants of the cost-effectiveness plane as a consequence of the small differences in costs and QALYs between the two arms (*Figure 12*). Overall, the probability that CRP testing is cost-effective at a willingness-to-pay threshold of £20,000 is 56% (*Figure 13*).

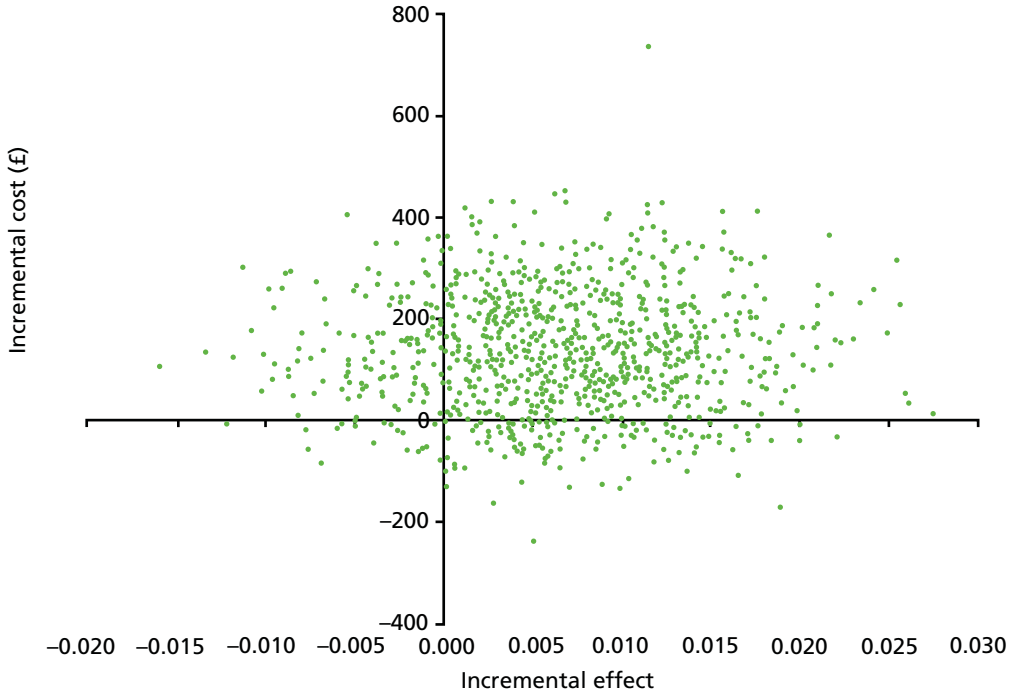

FIGURE 12 Cost-effectiveness plane (MITT analysis) for the base-case CUA (incremental cost per QALY gained).

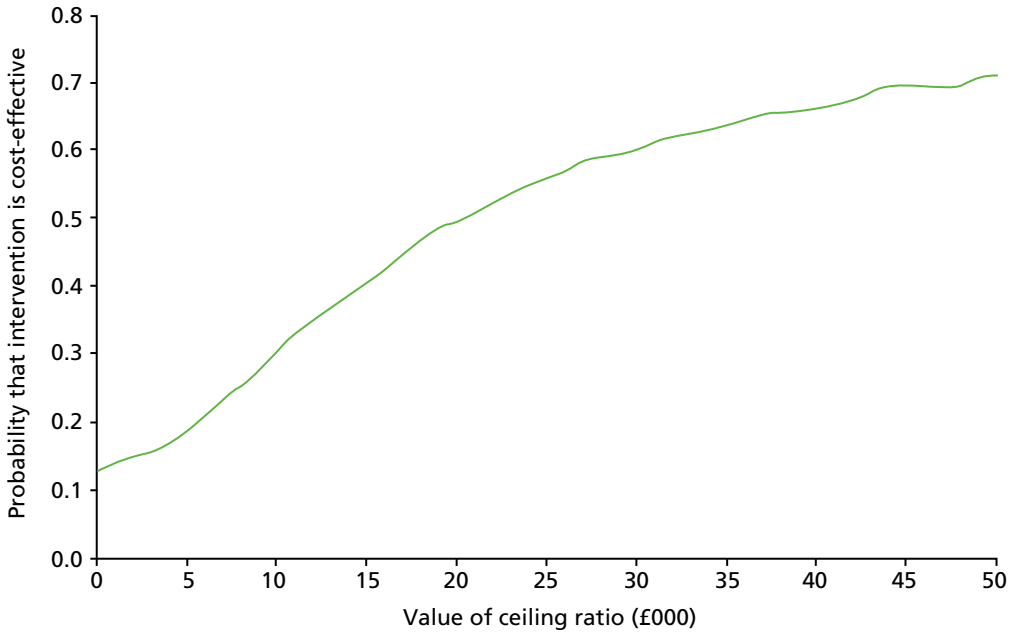

FIGURE 13 Cost-effectiveness acceptability curve (MITT analysis) for the base-case CUA (incremental cost per QALY gained).

Repeating the CUA using the ITT population after multiple imputation resulted in an ICER of £14,334. Using the lower and upper bounds of the 95% CIs for the cost and QALY differences to conduct deterministic sensitivity analysis results in ICERs between £7013 and £21,151, with scenarios in which the intervention is both dominating and dominated (*Table 27*). This high level of uncertainty is caused by the small differences in cost and especially the effect of the intervention compared with the control.

This is also illustrated by the cost-effectiveness plane (*Figure 14*), with point estimates distributed across all four quadrants. The majority of the point estimates indicate higher costs associated with the intervention, with most more effective than the control. The cost-effectiveness acceptability curve shows that, at a willingness-to-pay threshold of £20,000, the probability of the intervention's cost-effectiveness is 60% (*Figure 15*).

TABLE 27 Results of the deterministic sensitivity analyses on the ITT CUA results (following multiple imputation)

	Incremental			
Analysis	Cost (£)	Effect	ICER (£)	Quadrant
Base-case multiple imputation data	129.01 (95% CI –91.89 to 349.92)	0.009 (95% CI –0.002 to 0.020)	14,334	North-east quadrant (intervention more effective and more costly)
95% CI sensitivity analyses				
Upper bound cost Upper bound QALY	349.92	0.020	17,496	North-east quadrant (intervention more effective and more costly)
Upper bound cost Lower bound QALY	349.92	–0.002	(Not applicable) –174,959	North-west quadrant (intervention more costly and less effective: dominated)
Lower bound cost Upper bound QALY	–91.89	0.020	(Not applicable) –4595	South-east quadrant (intervention more effective and less costly: dominant)
Lower bound cost Lower bound QALY	–91.89	–0.002	45,946	South-west quadrant (intervention less effective and less costly)

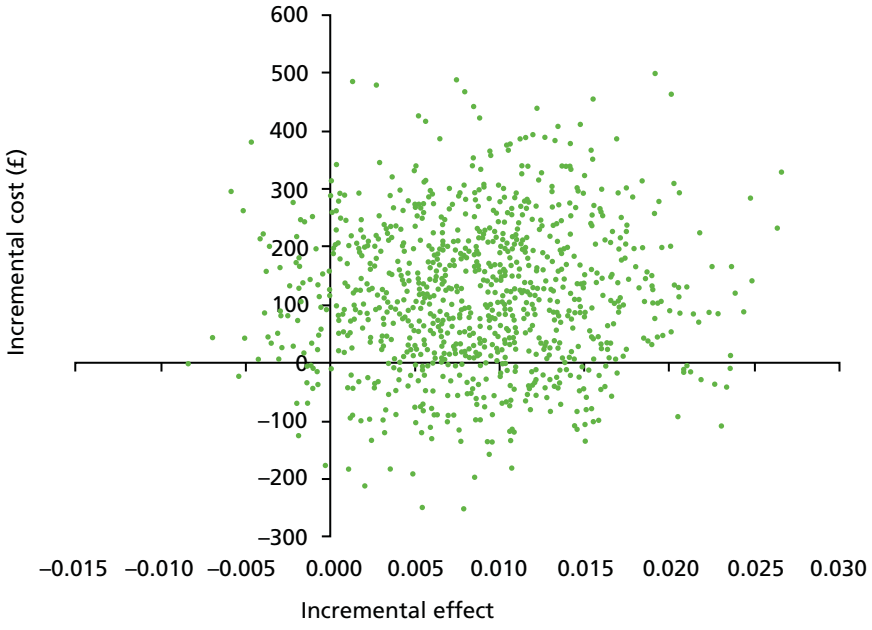

FIGURE 14 Cost-effectiveness plane (ITT analysis using multiple imputation) for the secondary CUA (incremental cost per QALY gained).

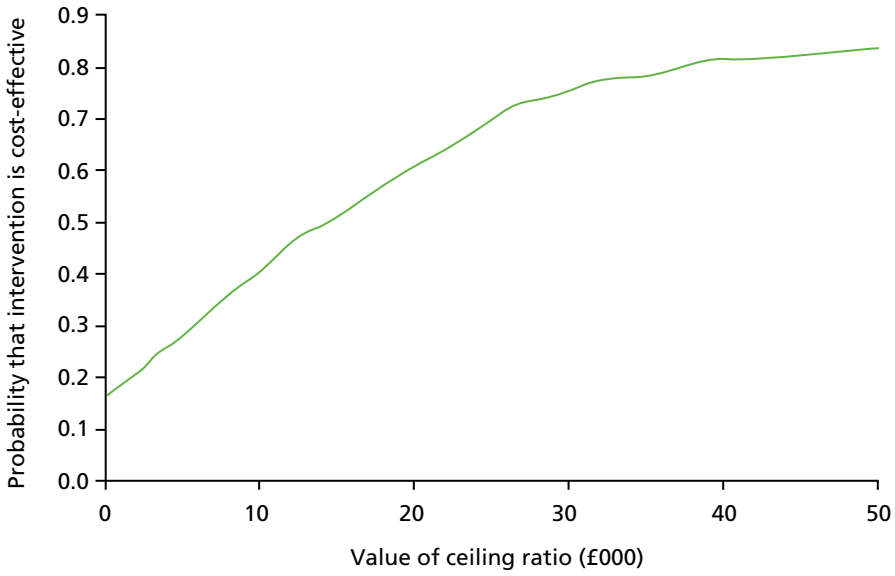

FIGURE 15 Cost-effectiveness acceptability curve (ITT analysis using multiple imputation) for the secondary CUA (incremental cost per QALY gained).

Cost–consequences analysis

Table 28 summarises the results of the cost–consequences analysis.

Budget impact analysis

The estimated budget impact of the use of CRP POCT in primary care is summarised in *Table 29*. During the 6-month trial period, the total cost per patient tested with CRP POCT was £126.26 (95% CI –£85.92 to £338.45) per patient higher than in the control arm. Extrapolated to the UK population, the estimated budget impact over 5 years is £534M (95% CI –£452.8M to £1.52B; see *Sensitivity analysis*). This is caused by increased hospitalisation costs in the CRP POCT arm, mostly unrelated to COPD.

TABLE 28 Clinical effectiveness and cost-effectiveness outcomes: cost–consequences analysis

Outcome	Trial arm		Difference (95% CI)	*p*-value
	CRP POCT	Usual care		
Cost impact (£)				
Total CRP POCT implementation costs	3924	34	3890	
Total costs at 4 weeks	46,778	40,935	5843	
Total costs at 6 months	238,000	196,358	41,642	
CRP POCT implementation costs per person	12.08	0.11	11.97 (11.60 to 12.34)	< 0.001
Mean cost at 4 weeks per patient	143.93	126.34	17.59 (–34.80 to 69.98)	0.408
Mean cost at 6 months per patient	732.31	606.04	126.26 (–85.92 to 338.45)	0.680
Mean COPD-related cost at 6 months per patient	294.14	287.33	6.81 (–116.49 to 130.11)	0.986
Total cost of productivity loss at 4 weeks	6746	13,981	7235	
Mean cost of productivity loss at 4 weeks per patient taking time off work	421.62	932.04	510.42 (–989.56 to –31.28)	0.022

continued

TABLE 28 Clinical effectiveness and cost-effectiveness outcomes: cost–consequences analysis (*continued*)

Outcome	Trial arm		Difference (95% CI)	*p*-value
	CRP POCT	Usual care		
Health impact				
Number (%) of patients consuming antibiotics for AECOPD in first 4 weeks	150 (57.0)	212 (77.4)	–62; AOR 0.31 (0.20 to 0.47)	< 0.001
Antibiotic prescribing at index consultation (%)	155 (47.7)	225 (69.7)	–70; AOR 0.31 (0.21 to 0.45)	< 0.001
Mean CCQ total scores (points)	2.6	2.8	–0.20 (–0.34 to –0.06)	0.005
EQ-5D health score (VAS)	62.9	59.8	3.12 (0.50 to 5.74)	0.019
QALYs in first 6 months	0.3000	0.2915	0.0085 (–0.0117 to 0.0286)	0.760
CRQ-SAS dyspnoea domain	4.3	4.2	0.06 (–0.20 to 0.33)	0.636
CRQ-SAS fatigue domain	3.6	3.5	0.13 (–0.12 to 0.38)	0.295
CRQ-SAS emotional function domain	4.4	4.3	0.15 (–0.04 to 0.34)	0.129
CRQ-SAS mastery domain	4.2	4.3	–0.09 (–0.18 to 0.01)	0.065
Adverse effects of treatment (%)	255 (89.5)	264 (91.3)	–9; AOR 0.79 (0.44 to 1.39)	0.410
Pneumonia diagnoses at 6 months (%)	9 (3.0)	12 (4.0)	–3; AOR 0.73 (0.29 to 1.82)	0.495

TABLE 29 Estimated costs associated with the use of CRP testing for COPD in primary care in the UK

Parameter	Year				
	1	2	3	4	5
Number of eligible patients (people diagnosed with COPD)	1,200,000	1,269,576	1,383,207	1,496,839	1,610,470
Uptake estimate (%)	10	20	30	40	50
CRP-tested patients	120,000	253,915	414,962	598,735	805,235
Yearly cost of CRP testing (£)	1,357,200	2,871,780	4,693,221	6,771,697	9,107,208
Yearly incremental cost of health-care use (£)	27,868,800	58,969,243	96,370,798	139,050,309	187,007,776
Net costs (£)	29,226,000	61,841,023	101,064,019	145,822,007	196,114,984

Sensitivity analysis

There is considerable uncertainty in the budget impact estimates. The 95% CIs around cost estimates are wide as a result of the general skewness of cost data. Using the 95% CI for secondary care costs as observed in the trial, the budget impact ranges from –£452.8M to £1.52B. Uptake rates are assumed as they are impossible to predict and any change will affect the budget impact of CRP testing. Assuming a stable uptake of 10%, 20%, 30%, 40% or 50% over 5 years results in budget impact estimates between £169.5M and £847.6M. Increasing the number of acute exacerbations per patient per year to two raises the budget impact estimate to £558.9M.

Finally, if COPD-related health-care costs only are considered in the budget impact analysis, CRP testing leads to a cost saving of £10.2M compared with current routine care. This is due to a health-care cost reduction of £7.98 per patient (95% CI –£138.55 to £122.59 per patient) in the CRP POCT arm as observed in the trial.

Summary

This chapter described, in detail, the methods and results of the health economic evaluation undertaken as part of the PACE trial. The results suggest that the use of CRP POCT in primary care reduces antibiotic consumption and costs without significantly affecting other COPD medication costs, health-care resource use and HRQoL. There were no significant differences in total incremental cost for all causes at 4 weeks or 6 months, or if only COPD-related health-care costs were considered in the analysis. The ICERs were £222 (95% CI –£42.00 to £518.14) per 1% reduction in antibiotic consumption and £15,251 (95% CI £2959 to £22,813) per QALY gained.

Chapter 6 Discussion

The PACE randomised controlled clinical trial found that using a CRP POCT to guide antibiotic prescribing decisions for patients presenting in primary care with an AECOPD resulted in an absolute reduction in antibiotic *consumption* over the 4 weeks after the initial consultation of 20%, and a marginal improvement in condition-specific health status that was smaller than the published, minimally important clinical significance for this outcome. Secondary outcomes, including antibiotic *prescribing* at the index consultation, antibiotic use for any reason, subsequent consultations in primary and secondary care, and COPD HRQoL and generic quality of life, were all consistent with the finding that the intervention safely reduced antibiotic use. Subgroup analyses suggest that the intervention effect was confined to patients with more than one Anthonisen criteria (the clinical features usually used to guide antibiotic treatment for AECOPD). There was no evidence of differences between the arms in the use of oral steroids or other relevant medications. Possible adverse effects from antibiotic consumption were reported by approximately 90% of participants, but there was no evidence of a difference between the trial arms. There was also no evidence that the intervention led to differences in antibiotic resistance in potential respiratory pathogens or commensal organisms isolated from sputum and throat swab samples 4 weeks after first consulting for the AECOPD.

The qualitative process evaluation found evidence that the CRP POCT was seen as broadly acceptable and useful by patients and primary care clinicians. Technical issues, such as the need to refrigerate cartridges and calibrate the machine, were seen as potential barriers to use, and concern about costs was a potential barrier to implementing the POCT in the context of NHS primary care services. Clinicians acknowledged that using the POCT increased consultation length, but they generally thought that this was offset by the perceived benefits. These benefits included reducing uncertainty in their prescribing decisions, using the test result to back up their prescribing decisions in discussions with patients and using the POCT as a tool to educate patients.

Our health economic evaluation found that the total cost from a NHS perspective at 4 weeks was < £20 more for patients managed with the addition of CRP POCT, and that there were no differences in total COPD-related costs between the two arms over 6 months.

Strengths and limitations

This pragmatic primary care trial was adequately powered to detect clinically important differences in both patient-reported antibiotic consumption and COPD health status at 2 weeks post randomisation. This is one of few studies of an antibiotic stewardship intervention to power on co-primary outcomes involving both a difference in antibiotic use and no worse (non-inferior) clinical outcomes. Patients were recruited during routine general practice consultations and from more than 80 UK general practices. Remote allocation was used and there was no evidence of breaches in allocation concealment. Participant characteristics, including age, comorbidities, smoking status, COPD health status and clinical features, were well balanced at baseline. Adherence to intervention allocation was good, with evidence that 97.5% of those allocated to CRP POCT received the test, and definitely < 3% received a CRP POCT at any point in the 4-week follow-up period. We ascertained initial antibiotic prescribing data for all but one participant. In addition, we ascertained patient-reported outcomes for > 80% of participants, with 83% and 87% of patients contributing data to the antibiotic use and COPD health status primary outcome analyses, respectively. We obtained follow-up data at 6 months for 68% of participants.

This was an open, pragmatic trial, with no blinding of participants or clinicians, as we aimed to assess the effects of the intervention in comparison with current usual practice. Introducing sham tests, for example, would have made comparison with usual care impossible. Open trials allow for a better measurement of the 'real-world' consequences of interventions. They are preferable for studies of cost-effectiveness as

knowledge of the intervention received may influence patients' decisions about subsequent help-seeking. Capturing subsequent resource use is critical to determining costs. However, the antibiotic prescribing reported by the responsible clinicians and captured from clinical records is consistent with patient-reported antibiotic use in the trial arms. It is possible that awareness of the intervention contributed to the beneficial impact we observed on COPD health status (e.g. through patients feeling better because they expected to feel better); if so, this effect would also occur in real-world clinical practice and, therefore, needed to be captured.[95]

We chose patient reports about antibiotic consumption (over the 4 weeks after the baseline appointment for their AECOPD) to be included in the co-primary outcome, rather than clinician reports or initial antibiotic prescribing data from the primary care clinical record. Antibiotics that are actually consumed, rather than prescribed, is the critical measure. 'Delayed' or 'back-up' antibiotic prescribing is relatively common for AECOPD, and antibiotics can be obtained from several sources, including hospitals, out-of-hours services and leftover antibiotics or 'rescue packs' of antibiotics stored at home. We captured both antibiotic prescribing and antibiotic use over 4 weeks to determine whether or not fewer initial prescriptions might have resulted in more subsequent reconsultations and further antibiotic prescribing.

Generalisability

Participants' age, gender, comorbidities and GOLD stage are in keeping with those of primary care patients with COPD,[96] and the potential pathogens isolated from baseline sputum samples are in keeping with those in other studies of AECOPD in the community.[89] Although all patients were assessed as having COPD by their recruiting clinician, and 97.5% of patients had a diagnosis of COPD in their medical records, we were able to obtain forced expiratory volume in 1 second (FEV_1) forced vital capacity (FVC) spirometry data for only 66% of participants from the primary care medical records and for many of these the spirometry was carried out many months before or after randomisation. However, clinicians tend to rely on the diagnosis in the medical records, rather than on a detailed review of spirometry results, when making treatment decisions for patients with AECOPD, hence the focus on having a COPD diagnosis in the clinical record, rather than on spirometry criteria, for trial eligibility.

The quality of spirometry is often suboptimal in primary care.[97] However, for those who had spirometry, the vast majority (85%) of patients met the criterion for the diagnosis of COPD. The decision to base inclusion on the recorded diagnosis and not on spirometry was explicit in the design. It was based on the already heavy burden of assessment on participating patients and practices and the pragmatic, 'real-world' nature of the trial. The low rate of recording of spirometry demonstrates how inappropriate it would have been to rely on general practice spirometry for the inclusion of patients. Most patients had purulent sputum, but only a minority (< 4%) had sputum that was rated as having the highest degree of purulence using the BronkoTest. This may be a reflection of the considerable variation of patients' interpretations of the BronkoTest in comparison with that of clinicians. Few participants had very severe underlying COPD in this study, so the findings may not be applicable to those with very severe COPD. We also excluded patients who had characteristics that may affect CRP levels (e.g. those with chronic inflammatory diseases) and those likely to be significantly immunocompromised, so our results cannot be generalised to these groups.

Interpretation and comparison with other literature

We searched MEDLINE using the search terms 'C-reactive protein/OR crp.mp' AND 'Pulmonary Disease, Chronic Obstructive/OR COPD.mp OR Respiratory Tract Infections/' AND 'Anti-Bacterial Agents/or antibiotic$.mp' and found three trials that used CRP POCT and included patients with COPD as part of their population. A Norwegian cluster randomised trial that recruited 179 patients with acute cough/LRTI comprised 29 patients with COPD or asthma.[98] The authors reported an overall reduction in antibiotic prescribing, but the study was not powered to detect a difference in the COPD/asthma group.

A Dutch cluster RCT that used a factorial design to randomise patients to CRP POCT or not, and to communication skills training or not, comprised 31 patients with COPD.[33] This study also found a significant reduction in antibiotic prescribing for LRTI, but it was also not powered for a subgroup analysis of patients with COPD. A non-randomised Spanish study of a multifaceted intervention consisting of audit and feedback, education and training in CRP testing for some clinicians found lower antibiotic 'overprescribing' for AECOPD (prescribing to patients with ≤ 2 Anthonisen criteria) by primary care clinicians who received training in CRP testing.[99] In the hospital setting, a meta-analysis of eight trials (1062 patients) found reasonable evidence for using procalcitonin to guide antibiotic initiation and discontinuation for AECOPD, with the aim of reducing antibiotic exposure without adversely affecting clinical outcomes.[100] There is a lack of similar trial evidence for CRP testing in the hospital setting, but observational studies have shown an association between higher CRP levels and pneumonia and benefit from antibiotics.[28,39] A recent Cochrane systematic review comprised six trials with > 3000 participants, and confirmed that CRP testing can safely reduce antibiotic prescribing for respiratory tract infections in the primary care setting.[101]

Although more than three-quarters of participants in our trial had ≥ 2 Anthonisen criteria, 76% of those in the intervention arm had a CRP level of < 20 mg/l, suggesting a low probability of significant bacterial infection and benefit from antibiotics. In the previous trial of antibiotics versus placebo for patients managed in the community with AECOPD from our group, we found no evidence of a between-arm difference in the proportions with clinical failure among those with a CRP level of < 40 mg/l.[24] Many patients with CRP levels in the 20–40 mg/l range, in addition to those with a CRP level of < 20 mg/l, could, therefore, probably be safely managed without antibiotics. We also found a 20% absolute reduction in antibiotic consumption despite antibiotics being prescribed for 33% of those with a CRP level of < 20 mg/l. These findings suggest, therefore, that our estimate of the potential reduction in antibiotic use from CRP POCT use is conservative.

Over half of the baseline sputa collected in our study did not yield any potential bacterial respiratory pathogen, and another one-fifth yielded both viral and bacterial pathogens (possible mixed infections). These findings are consistent with those of other studies, which have shown that bacterial infection is a likely trigger for AECOPD in a minority of patients[14] and, therefore, antibiotic treatment is unlikely to benefit many of them.

Antimicrobial stewardship is often promoted on the basis of the interests of future generations and society in general. However, taking fewer antibiotics may also benefit individuals by avoiding disruption of their microbiome,[16–18] including the selection of antimicrobial-resistant organisms that could lead to AECOPD that are more frequent and/or more difficult to treat. This could be especially important for patients with COPD who are at greater risk of being colonised with resistant pathogens than patients with normal lungs. At baseline, sputum sample bacteriology identified > 200 potential pathogens from the overall cohort; over one-third of the *H. influenzae* and *S. pneumoniae* strains cultured were not susceptible to ampicillin. However, in the trial, a comparison of the prevalence of resistant organisms isolated from patients at 4 weeks and resistance before treatment demonstrated no evidence of any beneficial effect of the intervention on antimicrobial resistance. Further planned analyses will explore differences in specific 'antibiotic–bacteria' combinations, and between those who did and those who did not consume antibiotics.

Antibiotics do benefit many people with AECOPD,[24] and the underprescribing of antibiotics needs to be avoided for patients who are likely to benefit. We included COPD health status in the co-primary outcome measure to assess whether or not any reduction in antibiotics might have occurred at the expense of patient recovery and well-being. Despite the important reduction in antibiotic use, we identified a small beneficial effect on condition-specific health status in the intervention arm. Possible explanations include a psychological benefit from the perceived benefits of a blood test to guide treatment, a reduction in adverse effects from antibiotics or beneficial effects from other interventions used instead of antibiotics. The last of these is unlikely, as we found no evidence of a difference in corticosteroid or inhaler use between the study arms. Furthermore, we found no evidence of benefits in terms of primary and secondary care consultations for any reason, or in disease-specific HRQoL during the 6-month follow-up period. However, a short-term (4 weeks) intervention (and in most cases a single antibiotic prescribing decision) is unlikely to have a dramatic effect on resistance or longer-term outcomes among patients who are frequently prescribed antibiotics.

Our qualitative findings are consistent with those of previous studies on the attitudes towards using CRP POCTs to manage LRTIs. Clinicians generally have positive views about using CRP POCTs to manage LRTIs, and feel that they provide an indication of disease severity, help manage patient expectations and increase their confidence in antibiotic-prescribing decisions.[67,102,103] Previous studies have also found similar concerns about the costs and implementation of CRP POCTs in the management of LRTIs in NHS primary care services.[68]

Our health economic evaluation identified reduced antibiotic costs at the initial consultation but no significant differences in the total incremental cost for all causes at 4 weeks or 6 months, or if only COPD-related health-care costs were considered in the analysis. To our knowledge, this is the first study reporting the cost-effectiveness of the use of CRP POCT in primary care to guide antibiotic prescribing for patients presenting with AECOPD based on actual antibiotic consumption. Three studies were identified that previously assessed the cost-effectiveness of CRP POCT for antibiotic prescribing in patients with LRTIs reporting similarly small cost and quality-of-life differences between groups.[35,36,104] Although these studies were conducted in different patient populations and settings, the similarities in the direction and magnitude of results confirms the robustness and accuracy of the cost-effectiveness evidence presented here.

Although we found increased all-cause health-care costs in the CRP POCT arm, these were largely attributed to a greater number of long-stay hospital patients, most of whom were admitted with conditions not related to their COPD. This might be an artefact of sampling variation or the low number of events rather than an indication of an underlying issue related to the intervention itself.

A limitation of the evaluation is the sensitivity of the cost–utility results to changes in patient quality of life. This is caused by the small differences in utility scores between the two arms. This could be caused by an insensitivity and lack of responsiveness of the generic EQ-5D instrument to small changes in the health status of specific conditions. However, EQ-5D-5L utility index values have been shown to correlate well with established disease-specific HRQoL questionnaires.[105] Furthermore, although the QALY difference at 6 months of 0.0085 does not reach the minimum important improvement of 0.05,[105] the PACE trial aimed to prove non-inferiority of health and QoL outcomes despite reduction in antibiotic consumption rather than superiority. This cost-effectiveness analysis is limited by the short follow-up of the trial, which could be addressed by long-term decision-analytic modelling based on the high-quality evidence produced by the PACE trial in the future.

Impact of patient and public involvement

Public contributors were an integral part of the study team from the very beginning of the research life cycle. Even before the first grant application was submitted, public contributors living with COPD helped develop the study question, they then contributed to the grant application itself and served on the Trial Management Group and the Trial Steering Committee. Throughout, they helped refine the study questions, contributed to critical decisions about the study outcomes, including which measures were most relevant to COPD patients; and ensured that patient-facing materials were readable and user friendly (including the CRFs and patient information leaflets) and that the research materials were simplified. For example, a critically important decision to change the scale used in the co-primary outcome was based largely on public contributor input. The contributors also helped produce regular study newsletters. Public contributors have also helped develop the dissemination strategy, and are advising on framing the main key messages and the implications of the results. After the pilot phase of the study, we met with a GP and respiratory nurse from one of the best recruiting practices in the pilot study and together identified items that could be removed from the baseline CRFs and instead included in the patient diary or 6-month medical record search CRF, to make the initial assessment less burdensome for busy clinicians who were delivering acute care while also recruiting to PACE. These modifications were fundamental to our ability to implement the full study, recruit to target and follow up participants so successfully.

Implications for clinical practice and future research

This pragmatic primary care trial provides clear evidence that using a CRP POCT to guide antibiotic treatment decisions for AECOPD is both clinically effective and cost-effective in safely reducing antibiotic use in those patients for whom antibiotics are not indicated. NICE already recommends the use of CRP testing to predict pneumonia in primary care.[86] We believe that our findings provide good evidence to support the use of a CRP POCT (with the associated guidance for clinicians that we used in this trial) to guide antibiotic-prescribing decisions for AECOPD in primary care.

Further research, building on our qualitative findings, could help understand how different implementation approaches affect POCT use and acceptability to both clinicians and patients of a CRP POCT for AECOPD in primary care. In addition, implementation studies are needed to determine the effect of this intervention on antibiotic use, clinical outcomes, antibiotic resistance in commensal organisms and help-seeking behaviour over the longer term. Although we found only small differences in short-term costs and no differences in long-term costs, there is a need to evaluate the health economic implications of the implementation of this intervention. Furthermore, the source of funding for any testing would need to be addressed before this test could be implemented into routine primary care.

Further research is also required to determine the added diagnostic and prognostic value of CRP for guiding AECOPD management, over and above the diagnostic and prognostic value of clinical features such as sputum colour, sputum volume, breathlessness and other biomarkers, and how various predictors are best combined. CRP self-testing is now a realistic possibility and could have a role in directing the self-management of 'rescue' antibiotics for some, but this will require further development and careful evaluation prior to implementation.

Conclusions

A CRP POCT to help guide antibiotic prescribing decisions for AECOPD in primary care is clinically effective and cost-effective in safely reducing antibiotic use and prescribing for patients with AECOPD, and is thus a useful adjunct to both improving outcomes for patients and enhancing antibiotic stewardship.

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Contributions of authors

Professor Nick A Francis (Professor of Primary Care Research, Primary Care and Public Health) was the co-chief investigator for the PACE trial. He contributed to the overall trial design and implementation, interpretation of findings, writing of the scientific summary and discussion section of the report, critical review of the report and final approval of the report submission.

Dr David Gillespie (Research Fellow in Statistics) was a co-investigator. He contributed to the trial design, conducted the statistical data analysis, wrote the methods and results sections, critically reviewed the report and gave final approval of the report.

Dr Patrick White (Senior Clinical Lecturer, Primary Care and Public Health Sciences) was a co-investigator. He contributed to the overall trial design and implementation, acquisition of data, interpretation of findings, critical review of the report and final approval of the report submission.

Janine Bates (Research Associate) was the trial manager, contributing to the trial design, the implementation and acquisition of data and the writing of the abstract, introduction and methods section of the report. She also co-ordinated the compilation, formatting, proofreading and final approval of the report.

Dr Rachel Lowe (Research Fellow) was the senior trials manager and the lead for trial management. She contributed to the trial design and implementation, acquisition of data, critical review of the report and final approval of the report submission.

Dr Bernadette Sewell (Senior Lecturer in Health Economics) contributed to the design of the health economics evaluation, conducted the health economics analysis, wrote the health economics evaluation section and gave final approval of the report.

Dr Rhiannon Phillips [Research Fellow, Primary and Emergency Care Research (PRIME) Centre Wales] was a co-investigator. She led the qualitative research, contributing to the study design, data analysis and interpretation, writing the qualitative evaluation section and critical review of the report and final approval of the report submission.

Helen Stanton (Research Assistant) contributed to the design and implementation of the qualitative research, acquisition and interpretation of data, critical review of the report and final approval of the report submission.

Nigel Kirby (Research Assistant) was the data manager. He contributed to the trial design, the implementation, acquisition and interpretation of data, critical review of the report and final approval of the report submission.

Dr Mandy Wootton (Lead Scientist/Operational Manager, Specialist Antimicrobial Chemotherapy Unit) was a co-investigator and the lead microbiologist. She contributed to the overall trial design, acquisition of data, interpretation of findings, writing of the microbiology sections of the report, critical review of the report and final approval of the report submission.

Dr Emma Thomas-Jones (Research Fellow) was the senior trials manager, contributing to the trial design and implementation, critical review of the report and final approval of the report submission.

Professor Kerenza Hood (Professor in Statistics and Director of Centre for Trials Research) was a co-investigator, contributed to the overall trial design and implementation, and supervised the statistical analysis and final approval of the report.

Dr Carl Llor (GP and senior researcher) was a co-investigator, contributing to the design and interpretation of the study, critical review of the report and final approval of the report submission.

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Professor Deborah Fitzsimmons (Professor of Health Outcomes Research and Academic Director, Swansea Centre for Health Economics) supervised the health economic analyses, review of the health economics evaluation section and final approval of the report.

Dr Mohammed Fasihul Alam (Assistant Professor in Health Economics) was a co-investigator and contributed to the design of the health economics evaluation and the final approval of the report submission.

Evgenia Riga (Clinical Trial Manager) was the trials manager at the Oxford centre and contributed to the design of the study, critical review of the report and final approval of the report submission.

Ann Cochrane (Research Fellow) was the trials manager at the London centre and contributed to the design of the study, acquisition of data, critical review of the report and final approval of the report submission.

Professor Christopher C Butler (NIHR Senior Investigator and Clinical Director of the University of Oxford Primary Care and Vaccines Clinical Trials Collaboration and the NIHR Oxford Community Medical Technology and Invitro Diagnostics Co-operative) was the co-chief investigator for the study. He contributed to the conception and overall design of the study, and the implementation and interpretation of the work. He contributed to the writing of the scientific summary and discussion section of the report, critical review of the report and final approval of the report submission.

Contributions of others

Other members of the trial team

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Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Clinical effectiveness methods

TABLE 30 Summary of outcomes and changes to the outcomes

Outcome measures	Time point(s) of evaluation of this outcome measure	Changes to outcome measures	Reason for the change
Primary			
Antibiotic consumption (any consumption of antibiotics for AECOPD vs. no consumption of antibiotics for AECOPD)	First 4 weeks post randomisation		
Recovery in terms of COPD health status as assessed using the CCQ total scores	2 weeks post randomisation		
Secondary			
Prevalence of potentially pathogenic bacteria [including *S. pneumoniae*, *Haemophilus species* spp and Enterobacteriaceae] cultured from sputum at 4 weeks and the proportion of bacteria that are resistant	4 weeks post randomisation		
Prevalence of commensal organisms cultured from throat swabs at 4 weeks and proportion of bacteria that are resistant	4 weeks post randomisation		
COPD health status over time measured using the CCQ total score	At weeks 1, 2 and 4 post randomisation		
CCQ symptoms domain	At weeks 1, 2 and 4 post randomisation		
CCQ function state domain	At weeks 1, 2 and 4 post randomisation		
CCQ mental state domain	At weeks 1, 2 and 4 post randomisation		
Total antibiotic consumption (number of days antibiotics consumed for AECOPD/any reason)	First 4 weeks post randomisation	Total antibiotic consumption (number of days antibiotics consumed for AECOPD/any reason) during first 4 weeks post randomisation was added in to secondary outcomes	
Health utility measured using the EQ-5D	At weeks 1, 2 and 4 and at 6 months post randomisation	EQ-5D was added to the 6-month postal follow-up Change from the EQ-5D-3L to the EQ-5D-5L	Owing to the more sensitive instrument becoming available at the time, the EQ-5D-3L used during the internal pilot was replaced by the EQ-5D-5L
All-cause antibiotic consumption	During the first 4 weeks post randomisation	All-cause antibiotic consumption during the first 4 weeks was added to the secondary outcomes	

continued

TABLE 30 Summary of outcomes and changes to the outcomes (*continued*)

Outcome measures	Time point(s) of evaluation of this outcome measure	Changes to outcome measures	Reason for the change
Antibiotic prescribing	At the index consultation		
Antibiotic prescribing	During the first 4 weeks post randomisation	Antibiotic prescribing during the first 4 weeks post randomisation was added to secondary outcomes	
Use of other COPD treatments including oral steroids	During the first 4 weeks post randomisation		
Adverse effects potentially attributable to antibiotics prescribed for the exacerbation	During the first 4 weeks post randomisation		
Primary and secondary care consultations, including hospitalisations	At week 4 and month 6		
Costs (total NHS cost) and cost-effectiveness	At month 6		
Incidence of pneumonia (measured by patient and GP report)	At week 4 and month 6		
Disease-specific HRQoL over time measured using CRQ-SAS (dyspnoea, fatigue, emotion function, mastery and total scores)	At month 6		

TABLE 31 Summary of changes to study inclusion criteria following the internal pilot

Pilot study inclusion/ exclusion criterion	Change made following pilot	Reason for change
Required spirometry confirmation of COPD, very severe (GOLD grade IV) excluded	Diagnosis of COPD in medical record: all COPD severities included, but those with a past history of respiratory failure or requiring mechanical ventilation excluded	This change occurred after the study had opened to recruitment in order to minimise the time taken for the initial assessment during times of delivering busy acute clinical care
Exclusion of those who had used systemic antibiotics in the past 4 weeks	Exclusion of those currently on antibiotics or who had taken antibiotics previously for the current AECOPD	Initially, those who had recently taken antibiotics were excluded as this would have had an impact on baseline assessments of antimicrobial resistance. We considered that the evidence generated by the study should be applicable to those who have recently had antibiotics
Exclusion of those with a life-limiting malignancy	No longer an exclusion criterion	We considered that the experimental intervention should be applicable to these patients
Exclusion of those who had taken systemic corticosteroids in the past week	No longer an exclusion criterion	We considered that the experimental intervention should be applicable to these patients

TABLE 32 Pilot study: eligibility criteria

Inclusion criteria	Exclusion criteria
Has spirometry-confirmed (post-bronchodilator FEV_1/FVC of < 0.7) mild, moderate or severe (GOLD grade I, II or III) COPD (FEV_1 of ≥ 30% predicted)	Very severe GOLD grade IV COPD (FEV_1 of < 30% predicted) or has a past history of respiratory failure or mechanical ventilation
Has a current AECOPD with presence of at least one of the following features: increased dyspnoea, increased sputum volume, increased sputum purulence	Has used systemic antibiotics in the last 4 weeks
Has AECOPD that has lasted for at least 24 hours and at most 21 days	The responsible clinician feels that urgent referral to hospital is necessary
Is aged ≥ 40 years	Has severe illness (e.g. suspected pneumonia, tachypnoea of > 30 breaths per minute, respiratory failure)
Is able to provide informed consent	Has a concurrent infection at another site (e.g. UTI, cellulitis) that is likely to produce a systemic response
	Has a chronic inflammatory condition (e.g. rheumatoid arthritis, polymyalgia rheumatica)
	Has a life-limiting malignancy
	Has taken systemic corticosteroids (e.g. oral tablets, injections) in the past week (not including systemic corticosteroids prescribed at baseline assessment)
	Has cystic fibrosis, a current tracheostomy or bronchiectasis of origin other than COPD
	Is immunocompromised (e.g. AIDS, taking immunosuppressive therapy or is receiving anticancer radiotherapy or chemotherapy)
	Is currently pregnant
	Has previously been recruited to the PACE study

AIDS, acquired immunodeficiency syndrome; UTI, urinary tract infection.

TABLE 33 Main study: eligibility criteria

Inclusion criteria	Exclusion 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	The responsible GP feels that urgent referral to hospital is necessary
Has a diagnosis of COPD in clinical record/on a COPD practice register	Has severe illness (e.g. suspected pneumonia, tachypnoea of > 30 breaths per minute, respiratory failure)
Is aged ≥ 40 years	Has concurrent infection at another site (e.g. UTI, cellulitis) that is likely to produce a systemic response
Is able to provide informed consent	Has a past history of respiratory failure or mechanical ventilation
Is able to provide the primary outcome data at 2 and 4 weeks within the expected windows	Is currently on antibiotics or has had antibiotics for this acute exacerbation of COPD
	Has an active inflammatory condition (e.g. flare-up of rheumatoid arthritis, gout or polymyalgia rheumatica)
	Has cystic fibrosis, a current tracheostomy or bronchiectasis
	Is immunocompromised (e.g. AIDS, taking systemic immunosuppressive therapy or receiving anticancer radiotherapy or chemotherapy)
	Is currently pregnant

AIDS, acquired immunodeficiency syndrome; UTI, urinary tract infection.

TABLE 34 Interpretation of CRP results

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

Assessment of sputum purulence

- Patient-reported sputum colour is often not reliable.
- Purulence can be increased in viral infections as well as bacterial infections.
- Try and obtain a sputum sample to objectively assess sputum purulence when 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.
- The CRP test is particularly useful when the presence of increased purulence is uncertain.

TABLE 35 Protocol changes

Amendment number	Details of changes made
1	Minor changes and addition of further clarification regarding the future use of the samples and the disposal of the capillary tube for the finger prick
2	Change of primary outcome measure from CRQ-SAS at 2-week follow-up to CCQ at 2-week follow-up. Addition of CRQ-SAS at 6-month follow-up
	Inclusion/exclusion criteria rephrasing and some additions
	Expansion on qualitative evaluation process
	Alteration to microbiological analysis
	Change to patient information sheet to add that we will collect participant's address
3	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 FEV_1/FVC of < 0.7) mild, moderate or severe COPD (GOLD grade I, II and III) to spirometry-confirmed mild, moderate or severe (GOLD grade I, II or III) COPD (FEV_1 of ≥ 30% predicted)
	Clarifying that the primary objective and primary outcome is antibiotic use for AECOPD
	All-cause antibiotic consumption during the first 4 weeks has been added to the secondary objectives, outcomes and analysis sections
	EQ-5D-5L has been added to the 6-month postal follow-up
	The CRP guidance has been corrected to the following categories: < 20, 20–40, > 40 mg/l
	Clarifying the safety reporting procedures
	New investigator (Carl Llor) and new administrator (Christian Barlow) have been added

TABLE 35 Protocol changes (*continued*)

Amendment number	Details of changes made
4	Clarify that the secondary outcome is prevalence of resistant bacteria in throat swab
	Change from the EQ-5D-3L to the EQ-5D-5L
	Inclusion/exclusion criteria rephrasing and some additions
	Clarification that the randomisation says 'usual care' not 'no POCT'
	Amend typographical error on back-up randomisation telephone number
	Amend 4-week follow-up window from –3 days to +14 days from +7 days
5	Clarification that Alere will provide training only to those practices using an Alere CRP machine
	Demographic data, FEV_1, 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 (e.g. views on the CRP test, research processes and management of COPD)
6	Six-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 out has been increased from 2 weeks (post 4-week follow-up date) to 4 weeks
7	Rephrasing of the secondary outcome measures
	Clarifying the quantitative process evaluation
	Clarifying procedures occurring at baseline and at follow-ups
	Clarification around statistical analyses
	Rephrasing of microbiological analyses
	Rephrasing of economic evaluation

Appendix 2 Clinical effectiveness results

Full intention-to-treat analysis (assuming data are missing at random)

A full ITT analysis was conducted for the co-primary outcomes, with participants with missing outcome data included using multiple imputation. The imputation models contained variables included in the original co-primary analyses (i.e. the Anthonisen criteria and, for the CCQ analysis, the baseline CCQ total score). Twenty imputations were run. For the primary CCQ analysis, 14 missing baseline CCQ scores were imputed using the mean of the valid responses.

The findings in *Tables 36* and *37* demonstrate that the adjustment made little difference to the intervention effect estimates, and the conclusions remain unaltered on the basis of these analyses.

Further sensitivity analysis adjusting analyses for missing data (assuming that data are missing not at random)

The observed mean CCQ total score at 2 weeks post randomisation was 2.7 points, with the mean 0.2 points higher (worse) in the control arm than in the CRP arm (*Table 38*). *Figure 16* demonstrates that the conclusions that can be drawn from the primary CCQ analysis are robust to all but the most extreme and implausible assumptions regarding missing participants (i.e. that missing control participants are identical to those observed and that missing CRP participants were over 3 points worse than those observed).

TABLE 36 Adjusted primary antibiotic analysis for missing data

Analysis set	*n*	AOR (95% CI)	*p*-value
MITT	537	0.31 (0.20 to 0.47)	< 0.001
Full ITT	649	0.33 (0.21 to 0.52)	< 0.001

TABLE 37 Adjusted primary CCQ analysis for missing data

Analysis set	*n*	AMD (90% CI)	*p*-value
MITT	563	–0.19 (–0.33 to –0.05)	0.023
MITT with missing baseline CCQ imputed via mean substitution	577	–0.20 (–0.34 to –0.06)	0.017
Full ITT	649	–0.20 (–0.36 to –0.04)	0.016

TABLE 38 Descriptive statistics for CCQ total score at 2 weeks post randomisation for participants who are included in the MITT analysis[a]

	Trial arm		
	Usual care	CRP POCT	Total
Observed, *n* (% total)	289 (89.2)	288 (88.6)	577 (88.9)
Missing, *n* (% total)	35 (10.8)	37 (11.4)	72 (11.1)
Observed (mean)	2.8	2.6	2.7
Observed (SD)	1.29	1.23	1.26

a Missing baseline CCQ total scores imputed using mean substitution.

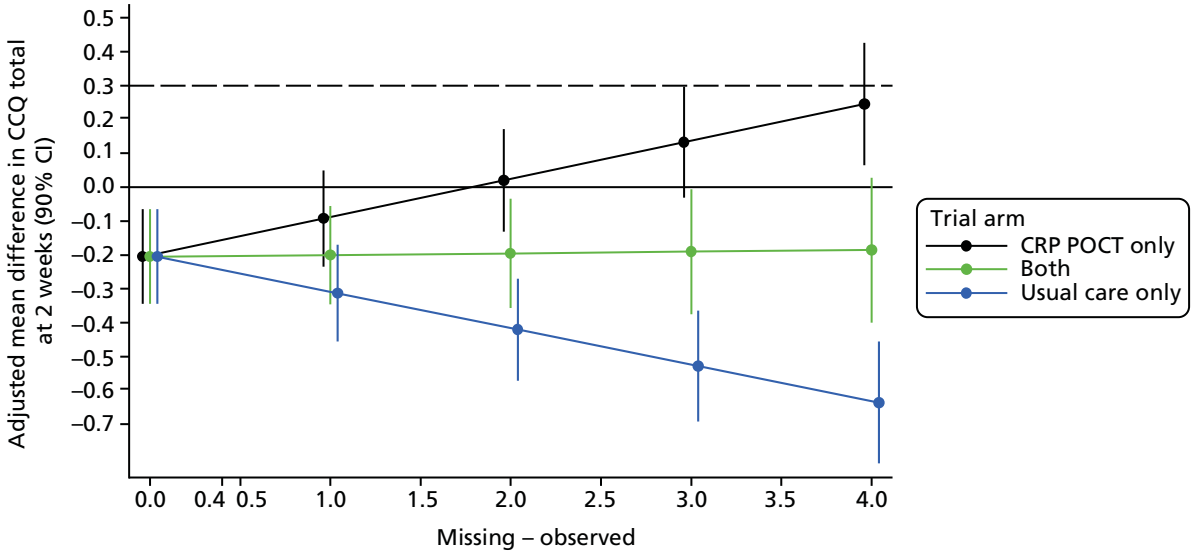

FIGURE 16 Impact of different missing data assumptions on the findings of the primary CCQ analysis. The figure is based on a series of pattern mixture models with mean in unobserved outcome minus mean in observed outcome ranging from 0 (missing at random assumption) to 4 (missing not at random assumption). Black solid line is at $y = 0$ (no difference between trial arms) and black dashed line is at $y = 0.3$ (non-inferiority margin).

Table 39 demonstrates that, for all but the most extreme and implausible assumptions (i.e. that missing CRP participants all consumed antibiotics and missing control participants did not), the conclusions drawn on the primary antibiotic analysis remain robust to various missing data assumptions.

Analysis accounting for change in eligibility criteria

The models presented in *Tables 40* and *41* suggest that, although there is a suggestion of a difference in outcomes before/after the change in eligibility criteria, this is independent of trial arm. The conclusions drawn regarding differences between trial arms remain unaltered when controlling for this change in eligibility criteria, and there is insufficient evidence to suggest that the intervention worked differently pre or post change.

Primary analysis on per-protocol population

Excluding participants from the co-primary analyses who were not eligible at the time of recruitment, or (for the primary CCQ analysis) did not provide data within the specified time window for data collection at 2 weeks post randomisation (–1 day/+7 days), did not appreciably change the intervention effect estimates and did not alter the conclusions that could be drawn regarding the co-primary outcomes (*Tables 42* and *43*).

TABLE 39 Best- and worst-case scenarios for missing primary antibiotic consumption for AECOPD data

Analysis	*n*	Trial arm, antibiotics, *n* (%)		AOR (95% CI)	*p*-value
		Control	CRP POCT		
MITT	537	212 (77.4)	150 (57.0)	0.31 (0.20 to 0.47)	< 0.001
Sensitivity 1: all non-responders used antibiotics	649	262 (80.9)	212 (65.2)	0.39 (0.27 to 0.58)	< 0.001
Sensitivity 2: all non-responders did not use antibiotics	649	212 (65.4)	150 (46.2)	0.39 (0.27 to 0.55)	< 0.001
Sensitivity 3: non-responders used antibiotics if prescribed them at index consultation	649	246 (75.9)	169 (52.0)	0.28 (0.19 to 0.41)	< 0.001
Sensitivity 4: non-responders in CRP arm used antibiotics and those in control arm did not use antibiotics	649	212 (65.4)	212 (65.2)	0.94 (0.66 to 1.33)	0.728

TABLE 40 Between-arm comparison of antibiotics consumed for AECOPD during the first 4 weeks post randomisation, adjusting for change in eligibility

Model	Variable	AOR (95% CI)	*p*-value
Without interaction	Before change in eligibility	Reference category for change in eligibility	0.065
	After change in eligibility	1.97 (0.96 to 4.04)	
	Control	Reference category for trial arm	< 0.001
	CRP POCT	0.31 (0.20 to 0.47)	
With interaction	After change in eligibility (main effect)	3.01 (1.19 to 7.59)	0.020
	CRP POCT (main effect)	0.67 (0.21 to 2.19)	0.511
	CRP POCT × after change in eligibility	0.41 (0.12 to 1.43)	0.162

TABLE 41 Between-arm comparison of CCQ total score at 2 weeks post randomisation, adjusting for change in eligibility

Model	Variable	AMD (95% CI)	*p*-value
Without interaction	Before change in eligibility	Reference category for change in eligibility	0.034
	After change in eligibility	–0.32 (–0.62 to –0.03)	
	Control	Reference category for trial arm	0.024
	CRP POCT	–0.19 (–0.35 to –0.03)	
With interaction	After change in eligibility (main effect)	–0.43 (–0.83 to –0.04)	0.032
	CRP POCT (main effect)	–0.40 (–0.93 to 0.13)	0.137
	CRP POCT × after change in eligibility	0.24 (–0.32 to 0.79)	0.406

TABLE 42 Primary antibiotic analysis for per-protocol analysis population

Analysis set	*n*	AOR (95% CI)	*p*-value
MITT	537	0.31 (0.20 to 0.47)	< 0.001
Per protocol	525	0.27 (0.18 to 0.43)	< 0.001

TABLE 43 Primary CCQ analysis for per-protocol analysis population

Analysis set	*n*	AMD (90% CI)	*p*-value
MITT	563	–0.19 (–0.33 to –0.05)	0.023
Per protocol	547	–0.19 (–0.32 to –0.05)	0.028

Medication consumption over time

The models in *Table 44* demonstrate that the consumption of antibiotics for AECOPD declines considerably during the follow-up period and is lower in participants allocated to the CRP arm. There is also some evidence of a differential intervention effect over time. This is best illustrated in *Figure 17*, which indicates a steeper decline in antibiotic consumption for control participants between weeks 1 and 2 (than for CRP participants), and a further decline between weeks 2 and 4 (whereas the proportion of participants in the CRP arm consuming antibiotics remains stable). The findings from these models are similar to those from the models exploring all-cause antibiotic consumption over time (*Table 45*).

TABLE 44 Antibiotics consumed for AECOPD over time[a]

Model	Variable	AOR (95% CI)	*p*-value
Without interaction	Week 1	Reference category for time point	< 0.001
	Week 2	0.10 (0.07 to 0.15)	
	Week 4	0.07 (0.05 to 0.10)	
	Control	Reference category for trial arm	< 0.001
	CRP POCT	0.46 (0.33 to 0.65)	
With interaction	Week 1	Reference category for time point main effect	< 0.001
	Week 2	0.07 (0.05 to 0.12)	
	Week 4	0.04 (0.02 to 0.07)	
	Control	Reference category for trial arm main effect	< 0.001
	CRP POCT	0.29 (0.19 to 0.46)	
	Week 2 × CRP POCT	1.85 (0.98 to 3.50)	0.005
	Week 4 × CRP POCT	3.00 (1.53 to 5.86)	

a Analysis based on 1672 responses from 614 participants in 84 practices. Model adjusts for Anthonisen criteria.

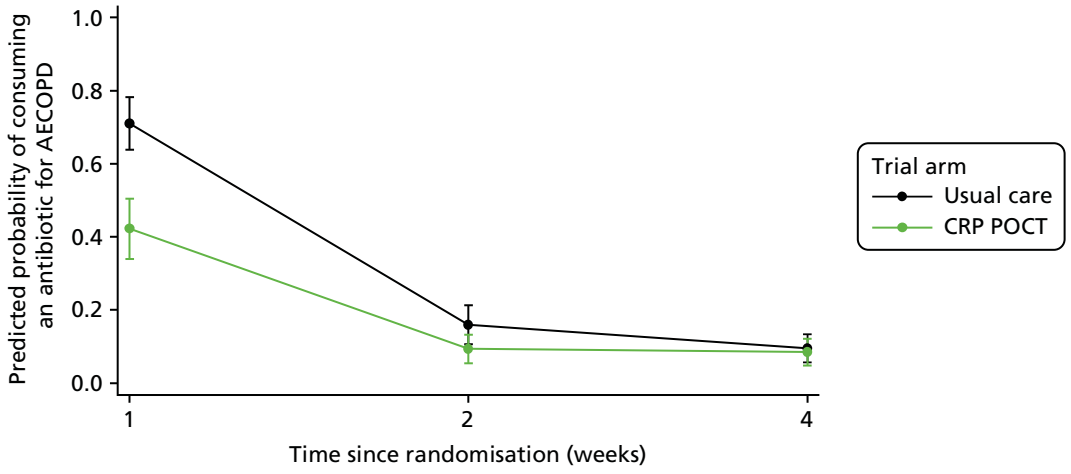

FIGURE 17 Predicted probabilities of antibiotic consumption for AECOPD over time, by trial arm.

TABLE 45 Antibiotics consumed for any reason over time[a]

Model	Variable	AOR (95% CI)	*p*-value
Without interaction	Week 1	Reference category for time point	< 0.001
	Week 2	0.12 (0.09 to 0.17)	
	Week 4	0.08 (0.06 to 0.12)	
	Control	Reference category for trial arm	< 0.001
	CRP POCT	0.48 (0.34 to 0.66)	
With interaction	Week 1	Reference category for time point main effect	< 0.001
	Week 2	0.09 (0.06 to 0.14)	
	Week 4	0.05 (0.03 to 0.08)	
	Control	Reference category for trial arm main effect	< 0.001
	CRP POCT	0.30 (0.19 to 0.47)	
	Week 2 × CRP POCT	1.92 (1.04 to 3.52)	0.006
	Week 4 × CRP POCT	2.79 (1.46 to 5.32)	

a Analysis based on 1696 responses from 615 participants within 84 practices. Model adjusts for Anthonisen criteria.

The model estimates presented in *Table 46* indicate that, although the use of other COPD medication declines considerably over the follow-up period, there is no evidence to suggest a difference between arms and, indeed, no evidence of any differential intervention effect over time (*Figure 18*).

TABLE 46 Use of other COPD treatments over time[a]

Model	Variable	AOR (95% CI)	*p*-value
Without interaction	Week 1	Reference category for time point	< 0.001
	Week 2	0.23 (0.17 to 0.33)	
	Week 4	0.06 (0.04 to 0.09)	
	Control	Reference category for trial arm	0.301
	CRP POCT	0.84 (0.61 to 1.16)	
With interaction	Week 1	Reference category for time point main effect	< 0.001
	Week 2	0.24 (0.15 to 0.39)	
	Week 4	0.05 (0.03 to 0.09)	
	Control	Reference category for trial arm main effect	0.357
	CRP POCT	0.77 (0.45 to 1.33)	
	Week 2 × CRP POCT	0.93 (0.49 to 1.75)	0.405
	Week 4 × CRP POCT	1.35 (0.71 to 2.59)	

a Analysis based on 1691 responses from 615 participants within 84 practices. Model adjusts for Anthonisen criteria.

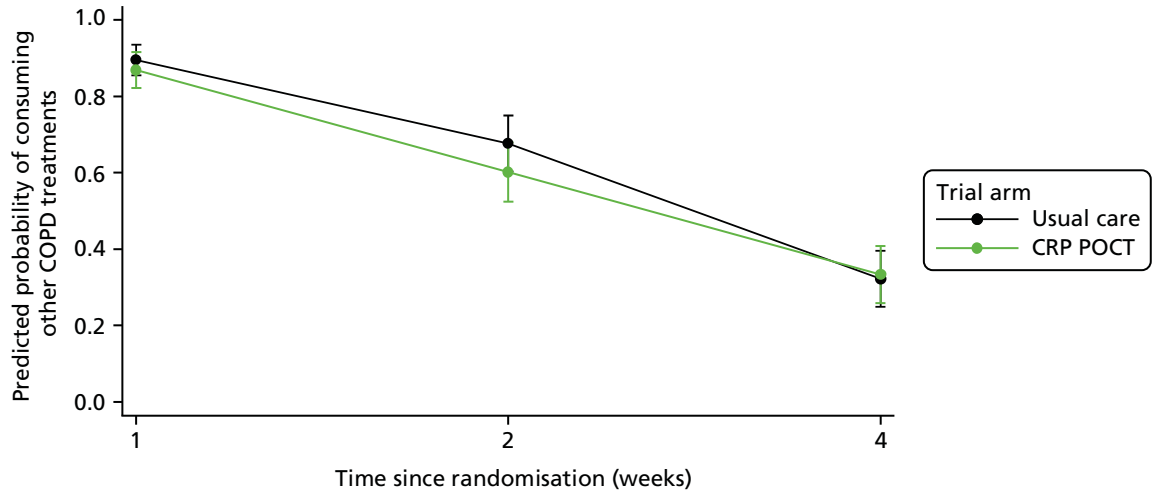

FIGURE 18 Use of other COPD treatments over time.

Rates of primary and secondary care consultations during the 6 months post randomisation

The distributions of primary and secondary care consultations during the first 6 months following randomisation for each trial arm are displayed in *Figures 19* and *20*.

The mean number of primary care consultations during the 6 months following randomisation was 6.3 (SE 0.28) for participants allocated to the control arm and 6.6 (SE 0.29) for participants allocated to the CRP POCT arm. The adjusted incidence rate ratio was 1.04 (95% CI 0.92 to 1.18; $p = 0.504$). The mean number of secondary care consultations during the 6 months following randomisation was 1.7 (SE 0.12) for participants allocated to the control arm and 1.6 (SE 0.11) for participants allocated to the CRP POCT arm. The adjusted incidence rate ratio was 0.96 (95% CI 0.79 to 1.17; $p = 0.719$). The mean number of primary and secondary care consultations combined was, therefore, a combination of the two separate consultation variables and, similarly, indicated no evidence of a difference between the arms (*Table 47*).

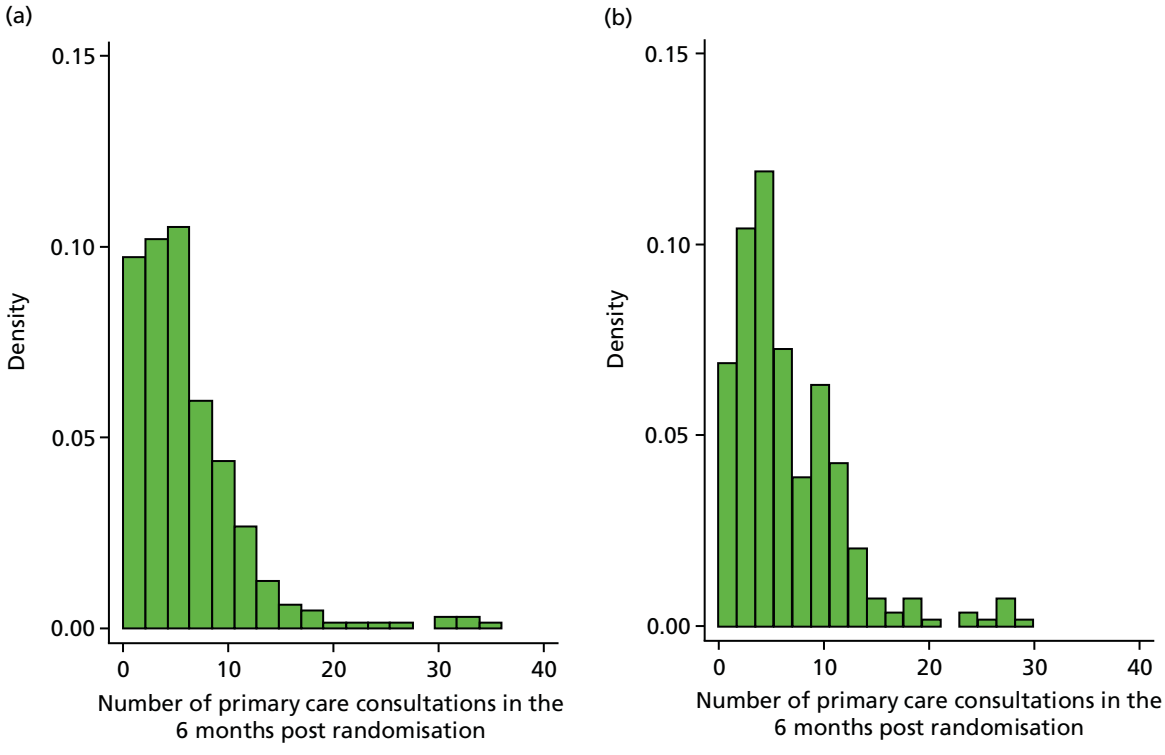

FIGURE 19 Distribution of number of primary care consultations by arm. (a) Usual care; and (b) CRP POCT.

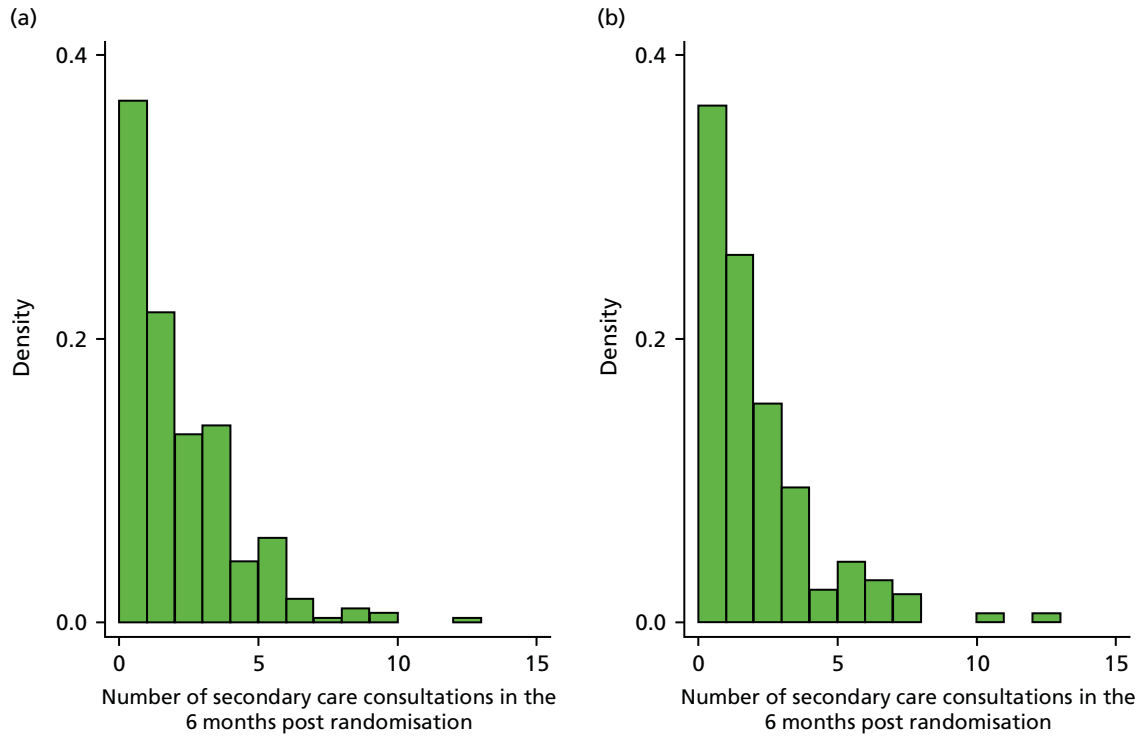

FIGURE 20 Distribution of number of secondary care consultations by arm. (a) Usual care; and (b) CRP POCT.

TABLE 47 Rates of primary and secondary care consultations during the 6 months post randomisation

Outcome measure	Time point	Trial arm: Usual care *n*	Usual care Mean (SE)	CRP POCT *n*	CRP POCT Mean (SE)	Adjusted incidence risk ratio[a] (95% CI)	*p*-value
Primary care consultations	Six months post randomisation	301	6.3 (0.28)	304	6.6 (0.29)	1.04 (0.92 to 1.18)	0.504
Secondary care consultations	Six months post randomisation	302	1.7 (0.12)	305	1.6 (0.11)	0.96 (0.79 to 1.17)	0.719
Primary and secondary care consultations	Six months post randomisation	302	7.9 (0.34)	305	8.2 (0.35)	1.02 (0.91 to 1.15)	0.726

a Ratio is CRP POCT/control. Adjusted for Anthonisen criteria. Clustering of participants within practices was accounted for by fitting a two-level linear regression model (analysis based on a maximum of 607 participants in 80 practices). For primary care consultations analysis, a negative binomial regression was fitted to account for overdispersed count data.

Prespecified subgroup analysis for the Clinical COPD Questionnaire primary outcome

There was no evidence of any differential intervention effects for the primary CCQ outcome for any of the prespecified subgroups (*Table 48*).

TABLE 48 Subgroup analyses for antibiotic consumption for CCQ total score at 2 weeks post randomisation (primary outcome)[a]

Subgroup analysis	Variable	AMD (95% CI)	*p*-value
COPD severity (GOLD category) (*n* = 351)	Usual care	Reference category for trial arm main effect (i.e. effect of trial arm for GOLD I subgroup)	0.140
	CRP POCT	–0.50 (–1.16 to 0.16)	
	GOLD I	Reference category for COPD severity main effect (i.e. effect of GOLD subgroup for participants allocated to usual-care arm)	0.256
	GOLD II	–0.22 (–0.72 to 0.28)	
	GOLD III	0.02 (–0.52 to 0.56)	
	GOLD IV	0.22 (–0.45 to 0.90)	
	CRP POCT × GOLD I	Reference category for trial arm × COPD severity interaction	0.793
	CRP POCT × GOLD II	0.30 (–0.42 to 1.01)	
	CRP POCT × GOLD III	0.29 (–0.48 to 1.06)	
	CRP POCT × GOLD IV	0.00 (–1.05 to 1.05)	
Severity of COPD exacerbation (Anthonisen criteria) (*n* = 563)	Usual care	Reference category for trial arm main effect (i.e. effect of trial arm for 1/3 features subgroup)	0.737
	CRP POCT	–0.06 (–0.39 to 0.28)	
	1/3 features	Reference category for severity of COPD exacerbation main effect (i.e. effect of severity of COPD exacerbation for participants allocated to the usual-care arm)	0.564
	2/3 features	0.16 (–0.15 to 0.48)	
	3/3 features	0.13 (–0.16 to 0.43)	
	CRP POCT × 1/3 features	Reference category for trial arm × severity of COPD exacerbation interaction	0.627
	CRP POCT × 2/3 feature	–0.22 (–0.66 to 0.23)	
	CRP POCT × 3/3 feature	–0.15 (–0.56 to 0.27)	
Presence of potentially pathogenic bacteria cultured from sputum at baseline (*n* = 353)	Usual care	Reference category for trial arm main effect (i.e. effect of trial arm for no potential pathogenic bacteria subgroup)	0.263
	CRP POCT	–0.16 (–0.43 to 0.12)	
	No potential pathogenic bacteria	Reference category for the presence of potentially pathogenic bacteria cultured from sputum at baseline main effect (i.e. effect of presence of potential pathogenic bacteria for participants allocated to the usual-care arm)	0.286
	Potential pathogenic bacteria	0.16 (–0.14 to 0.46)	
	CRP POCT × no potential pathogenic bacteria	Reference category for trial arm presence of potential pathogenic bacteria interaction	0.538
	CRP POCT × potential pathogenic bacteria	–0.13 (–0.55 to 0.29)	

a Models adjust for Anthonisen criteria (when it is not the subgroup of interest) and CCQ total score at baseline.

Appendix 3 Health economics

Unit costs

TABLE 49 Unit costs of antibiotics and oral corticosteroids included in costing for the health economic evaluation

Medication	Dose (mg)	Pack size	Unit cost (£)
Antibiotics			
Amoxicillin	250	14	0.69
Amoxicillin	250	21	0.97
Amoxicillin	500	14	0.90
Amoxicillin	500	21	1.26
Azithromycin	250	4	1.25
Azithromycin	500	3	1.07
Cefalexin	250	28	1.44
Cefalexin	500	21	1.64
Ciprofloxacin	100	6	1.97
Ciprofloxacin	250	10	0.68
Ciprofloxacin	500	10	0.89
Ciprofloxacin	750	10	8.00
Ciprofloxacin	Eye drops	5 ml	4.70
Ciprofloxacin/dexamethasone	Ear drops	5 ml	6.12
Clarithromycin	250	14	1.20
Clarithromycin	500	14	2.01
Clarithromycin suspension	250 mg/5 ml	70 ml	4.66
Co-amoxiclav	375	21	1.66
Co-amoxiclav	625	21	1.73
Doxycycline	50	28	1.22
Doxycycline	100	8	0.78
Erythromycin	250	28	1.30
Flucloxacillin	250	28	1.25
Flucloxacillin	500	28	1.69
Macrobid	100	14	9.50
Metronidazole	200	21	1.49
Metronidazole	400	21	4.10
Metronidazole	500	21	37.82
Nitrofurantoin	50	28	13.43
Nitrofurantoin	100	28	8.57

continued

TABLE 49 Unit costs of antibiotics and oral corticosteroids included in costing for the health economic evaluation (*continued*)

Medication	Dose (mg)	Pack size	Unit cost (£)
Oxytetracycline	250	28	0.84
Phenoxymethylpenicillin	250	28	0.97
Trimethoprim	100	28	0.85
Trimethoprim	200	6	0.40
Trimethoprim	200	14	0.93
Oral corticosteroids			
Dexamethasone	2	50	16.41
Prednisolone	1	28	0.68
Prednisolone	5	28	0.74
Prednisolone	25	56	75.00

Source of unit costs: Monthly Index of Medical Specialities 2017[79] and *British National Formulary*.[80]

TABLE 50 Unit costs of inhaled medication included in costing for the health economic evaluation

Medication	Inhaler type	Dose per puff (mg)	Pack size (puffs)	Unit cost (£)
Aclidinium	Eklira Genuair (AstraZeneca UK Limited, Luton, UK)	322	60	28.60
Beclometasone	Clenil Modulite 50 (Chiesi Limited, Manchester, UK)	50	200	3.70
	Clenil Modulite 100	100	200	7.42
	Clenil Modulite 200	200	200	16.17
	Clenil Modulite 250	250	200	16.29
Formoterol	Atimos Modulite (Chiesi Limited, Manchester, UK)	12	100	30.06
	Formoterol Easyhaler [Orion Pharma (UK) Limited, Newbury, UK]	12	120	23.75
	Foradil (Novartis Pharmaceuticals UK Ltd, Camberley, UK)	12	60	28.06
	Oxis Turbohaler 6 (AstraZeneca UK Limited, Luton, UK)	6	60	24.80
	Oxis Turbohaler 12	12	60	24.80
Formoterol/ aclidinium	Duaklir Genuair (AstraZeneca UK Limited, Luton, UK)	12/340	60	32.50
Formoterol/ beclametasone	Fostair 100/6 (Chiesi Limited, Manchester, UK)	6/100	120	29.32
	Fostair 200/6	6/200	120	29.32
	Fostair NEXThaler 100/6	6/100	120	29.32
	Fostair NEXThaler 200/6	6/200	120	29.32
Formoterol/ budesonide	Symbicort 100/6 Turbohaler (AstraZeneca UK Limited, Luton, UK)	6/100	120	33.00
	Symbicort 200/6 Turbohaler	6/200	120	38.00
	Symbicort 400/12 Turbohaler	12/400	60	38.00
	Symbicort pMDI	6/200	120	28.00

TABLE 50 Unit costs of inhaled medication included in costing for the health economic evaluation (*continued*)

Medication	Inhaler type	Dose per puff (mg)	Pack size (puffs)	Unit cost (£)
Formoterol/ budesonide	DuoResp Spiromax 160/4.5 (Teva Pharma B.V., Swensweg, the Netherlands)	6/200	120	29.97
	DuoResp Spiromax 320/9	12/400	60	29.97
Formoterol/ fluticasone	Flutiform (Napp Pharmaceuticals Limited, Cambridge, UK)	5/50	120	14.40
	Flutiform	5/125	120	28.00
	Flutiform	10/250	120	45.56
Fluticasone	Flixotide Accuhaler 50 (GlaxoSmithKline UK, Uxbridge, UK)	50	60	4.00
	Flixotide Accuhaler 100	100	60	8.00
	Flixotide Accuhaler 250	250	60	25.51
	Flixotide Accuhaler 500	500	60	43.37
	Flixotide Evohaler 50	50	120	5.44
	Flixotide Evohaler 125	125	120	12.50
	Flixotide Evohaler 250	250	120	20.00
Glycopyrronium	Seebri Breezhaler (Novartis Pharmaceuticals Ltd, Dublin, Ireland)	50	30	27.50
Indacaterol	Onbrez Breezhaler (Novartis Pharmaceuticals Ltd, Dublin, Ireland)	150	30	32.19
	Onbrez Breezhaler	300	30	32.19
Indacaterol/ glycopyrronium	Ultibro Breezhaler (Novartis Pharmaceuticals Ltd, Dublin, Ireland)	110	10	10.83
	Ultibro Breezhaler	110	30	32.50
Ipratropium bromide	Atrovent (Boehringer Ingelheim Limited, Bracknell, UK)	20	200	5.56
	Ipratropium Steri-Neb (Teva UK Ltd, Harlow, UK)	250 ml	1 ml	4.71
	Ipratropium Steri-Neb	250 ml	2 ml	5.61
Olodaterol/ tiotropium	Spiolto Respimat (Boehringer Ingelheim Limited, Bracknell, UK)	2.5/2.5	60	32.50
Salbutamol	Airomir (Teva UK Ltd, Harlow, UK)	100	200	1.97
	Airomir Autohaler	100	200	6.02
	Easyhaler	100	200	3.31
	Salamol Easi-Breathe (Teva UK Ltd, Harlow, UK)	100	200	6.30
	Easyhaler	200	200	6.63
Salbutamol nebulised	Salamol Steri-Neb	2.5 mg/2.5 ml	20	1.91
	Salamol Steri-Neb	5 mg/2.5 ml	20	3.82
	Ventolin® Evohaler® (Glaxo Wellcome UK Limited, Uxbridge, UK)	100	200	1.50
	Ventolin® Accuhaler® (Glaxo Wellcome UK Limited, Uxbridge, UK)	200	60	3.60
Ventolin nebulised	Ventolin® Nebules® (Glaxo Wellcome UK Limited, Uxbridge, UK)	2.5 mg/2.5 ml	20	1.65
	Ventolin® Nebules®	5 mg/2.5 ml	20	2.78
Salmeterol	Neovent™ [Fannin (UK) Limited, Wellingborough, UK]	25	120	29.26
	Serevent® Evohaler® (Glaxo Wellcome UK Limited, Uxbridge, UK)	25	120	29.26
	Serevent® Accuhaler® (Glaxo Wellcome UK Limited, Uxbridge, UK)	50	60	35.11
	Vertine	25	120	23.40

continued

TABLE 50 Unit costs of inhaled medication included in costing for the health economic evaluation (*continued*)

Medication	Inhaler type	Dose per puff (mg)	Pack size (puffs)	Unit cost (£)
Salmeterol/ fluticasone	Seretide 100 Accuhaler (Glaxo Wellcome UK Limited, Uxbridge, UK)	50/100	60	18.00
	Seretide 250 Accuhaler	50/250	60	35.00
	Seretide 500 Accuhaler	50/500	60	40.92
	Seretide 100 Evohaler (Glaxo Wellcome UK Limited, Uxbridge, UK)	25/100	120	18.00
	Seretide 250 Evohaler	25/250	120	35.00
	Seretide 500 Evohaler	25/500	120	59.48
	Sirdupla [Generics (UK) Limited t/a Mylan, Potters Bar, UK]	25/125	120	26.25
	Sirdupla	25/250	120	44.61
	AirFluSal Forspiro (Sandoz Limited, Camberley, UK)	50/500	60	29.97
Terbutaline	Bricanyl® Turbohaler® (AstraZeneca UK Ltd, Luton, UK)	500	100	8.30
Tiotropium	Braltus (Teva UK Limited, Eastbourne, UK)	13	30	25.80
	Spiriva® (Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany)	18	30	34.87
	Spiriva Respimat	2.5	60	23.00
Umeclidinium	Incruse Ellipta [GlaxoSmithKline (Ireland) Limited, Dublin, Ireland]	55	30	27.50
Vilanterol/ umeclidinium	Anoro Ellipta [GlaxoSmithKline (Ireland) Limited, Dublin, Ireland]	22/55	30	32.50
Vilanterol/ fluticasone	Relvar Ellipta [GlaxoSmithKline (Ireland) Limited, Dublin, Ireland]	22/92	30	22.00
Vilanterol/ fluticasone	Relvar Ellipta	22/184	30	29.50
Aerochamber Plus			Device	4.90

Source of unit costs: Monthly Index of Medical Specialties 2017[79] and *British National Formulary* 2017.[80]

TABLE 51 Unit costs of health-care resources included in costing for the health economic evaluation[a,b]

Resource	Currency code	Unit cost (£)	Notes
Primary care			
GP consultation at surgery	N/A	36.00	9.22 minutes' duration including direct care staff and qualifications
GP consultation at home	N/A	85.00	GP home visit (9.22 minutes) plus 20 minutes' travel time (indirect, £147 per hour)
GP consultation by telephone	N/A	27.36	7.1 minutes' duration
Nurse consultation at surgery	N/A	9.46	£56.74 per hour (including qualifications), 10-minute appointment assumed
Nurse consultation at home	N/A	23.79	10 minutes at £56.74 per hour plus 20 minutes' travel time (indirect, £43 per hour)
Nurse consultation by telephone	N/A	6.71	7.1 minutes' duration
NHS Direct consultation	N/A	14.60	Costed as telephone triage (GP led)

TABLE 51 Unit costs of health-care resources included in costing for the health economic evaluation[a,b] (*continued*)

Resource	Currency code	Unit cost (£)	Notes
Secondary care			
A&E attendances			
Unspecified (all)	N/A	137.74	Weighted across all specialties according to frequency (number of attendances)
Discharged	N/A	115.10	
Admitted	N/A	194.12	
Outpatient attendances			
Addiction services	721	21.30	
Anticoagulant service	324	26.26	
Audiology	840	58.33	
Breast surgery	103	141.86	
Cardiology	320	127.67	
Chemical pathology	822	89.11	
Colorectal surgery	104	130.32	
Dermatology	330	101.63	
Diabetic medicine	307	159.31	
Diagnostic imaging	812	37.30	Assumed as X-ray
Endocrinology	302	157.74	
ENT	120	96.87	
Gastroenterology	301	136.57	
General medicine	300	167.05	
General surgery	100	130.06	
Geriatric medicine	430	220.29	
Gynaecology	502	133.01	
Haematology	303	160.58	
Hepatology	306	255.35	
Maxillofacial surgery	144	118.90	
Medical oncology	370	151.12	
Mental illness	710	287.57	
Nephrology	361	150.78	
Neurology	400	175.60	
Neurosurgery	150	205.98	
Old-age psychiatry	715	171.41	
Ophthalmology	460	63.46	
Oral surgery	140	111.47	
Pain management	191	139.12	
Plastic surgery	160	99.95	
Pharmacology	305	114.04	

continued

TABLE 51 Unit costs of health-care resources included in costing for the health economic evaluation[a,b] (*continued*)

Resource	Currency code	Unit cost (£)	Notes
Physiotherapy	650	48.33	
Palliative medicine	315	207.43	
Podiatry	653	42.84	
Programmed pulmonary rehabilitation	342	58.69	
Radiology	811	84.52	
Respiratory medicine	340	154.77	
Rheumatology	410	142.74	
Speech and language therapy	652	116.05	
Spinal surgery service	108	134.83	
Stroke medicine	328	170.60	
Thoracic surgery	173	194.31	
Transient ischaemic attack	329	179.57	
Trauma and orthopaedics	110	117.01	
Upper gastrointestinal surgery	106	131.80	
Urology	101	105.19	
Vascular surgery	107	153.01	
Inpatient stays			
Non-elective inpatient stay (no further information)		3058.19	Weighted across all specialties according to frequency (number of episodes), mean length of stay 7.87 days
Non-elective excess bed-day		298.41	Weighted, added per day for stays of > 8 days
Elective inpatient stay (no further information)		3749.81	Weighted across all specialties according to frequency (number of episodes), mean length of stay 4.72 days
Elective excess bed-day		361.67	Weighted, added per day for stays of > 5 days
Non-elective short stay (no further information)		615.83	Weighted across all specialties according to frequency (number of episodes), mean length of stay 1 overnight stay

ENT, ear, nose and throat surgery; N/A, not applicable.
a Curtis and Burns (Personal Social Services Research Unit) 2016.[78]
b Curtis and Burns (Personal Social Services Research Unit) 2015[106] (inflated).
All inpatient stays with reason/description were costed according to the indication using appropriate currency codes.

Results

TABLE 52 Total medication costs recorded for the CRP POCT and control arms during the trial follow-up period

Medication	Trial arm, total cost (£)		Difference (£)
	CRP POCT ($n = 325$)	Usual care ($n = 324$)	
Antibiotics			
Cost at index consultation	203.29	292.34	–89.05
Cost at 6-month review	668.33	617.80	50.53
Oral steroids			
Cost at index consultation	244.02	236.68	7.34
Cost at 6-month review	335.37	380.09	–44.72
Inhaled medications			
Cost at index consultation	1017.50	993.50	24.00
Cost at 6-month review	3053.75	2338.51	715.24
Total medication cost			
Cost at index consultation	1464.81	1522.52	–57.71
Cost at 6-month review	4057.45	3336.39	721.05

TABLE 53 Total primary care costs recorded for the CRP POCT and control arms for any reason during the trial follow-up period

Health-care resource	Trial arm (£)		Difference (£)
	CRP POCT ($n = 275$)	Usual care ($n = 280$)	
Primary care: total cost in 4-week follow-up period			
GP visits at surgery in 4 weeks' follow-up	3960.00	5076.00	–1116.00
Nurse visits at surgery in 4 weeks' follow-up	765.99	690.34	75.65
GP visits at home in 4 weeks' follow-up	340.00	425.00	–85.00
Nurse visits at home in 4 weeks' follow-up	23.79	47.58	–23.79
GP telephone consultations in 4 weeks' follow-up	820.80	1121.76	–300.96
Nurse telephone consultations in 4 weeks' follow-up	60.43	53.71	6.71
Other health-care contacts in 4 weeks' follow-up	511.00	467.20	43.80
Total cost of primary care use in 4 weeks' follow-up	6482.01	7881.59	–1399.58
Primary care: total cost in 6-month review period for any reason			
	$n = 304$	$n = 302$	
GP visits at surgery	35,748.00	34,524.00	1224.00
Nurse visits at surgery	5484.87	5049.86	435.01
GP visits at home	2125.00	2890.00	–765.00
Nurse visits at home	547.17	428.22	118.95
GP telephone consultations	8481.60	7633.44	848.16

continued

TABLE 53 Total primary care costs recorded for the CRP POCT and control arms for any reason during the trial follow-up period (*continued*)

Health-care resource	Trial arm (£)		Difference (£)
	CRP POCT ($n = 275$)	Usual care ($n = 280$)	
Nurse telephone consultations	423.00	396.14	26.86
Other contacts	85.14	66.22	18.92
Total cost of primary care use	52,894.77	50,987.88	1906.89
Primary care related to COPD: total cost in 6-month review period for COPD-related reasons			
GP visits at surgery	13,968.00	15,120.00	–1152.00
Nurse visits at surgery	2222.32	2014.27	208.05
GP visits at home	935.00	1360.00	–425.00
Nurse visits at home	0.00	333.06	–333.06
GP telephone consultations	3310.56	3392.64	–82.08
Nurse telephone consultations	248.43	228.28	20.14
Other contacts	28.38	47.30	–18.92
Total cost of primary care use	20,712.68	22,495.55	–1782.87

TABLE 54 Total secondary care costs recorded for the CRP POCT and control arms during the trial follow-up period

Health-care resource	Trial arm (£)		Difference (£)
	CRP POCT ($n = 275$)	Usual care ($n = 280$)	
Secondary care: total cost during the 4-week follow-up period			
A&E visits	1903.38	1433.78	469.60
Outpatient appointments	3988.74	5874.06	–1885.32
Inpatient stays	14,389.09	8804.48	5584.62
Other secondary care use	2212.75	2942.83	–730.08
Total cost of secondary care use	22,493.96	19,055.14	3438.82
Secondary care: total cost in the 6-month review period for any reason			
	$n = 305$	$n = 302$	
A&E visits	11,294.68	10,468.24	826.44
Outpatient appointments	46,356.10	47,568.97	–1212.87
Inpatient stays	106,046.95	70,106.45	35,940.50
Total cost of secondary care use	163,697.73	128,143.66	35,554.07
Secondary care related to COPD: total cost in the 6-month review period for COPD-related reasons			
A&E visits	4958.64	4407.68	550.96
Outpatient appointments	7337.58	11,127.03	–3789.45
Inpatient stays	40,919.04	37,317.07	3601.97
Total cost of secondary care use	53,215.26	52,851.78	363.48

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