C-Reactive Protein-guided antibiotic prescribing for COPD exacerbations: a qualitative evaluation

Running title: CRP-guided management of COPD exacerbations

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Clinical Trial Registration: ISRCTN24346473

Keywords: C-reactive protein, Chronic Obstructive Pulmonary Disease, antibiotic, point of care technology, primary health care, qualitative evaluation
How this fits in:
The PACE randomised controlled trial found that a C-reactive protein point-of-care test (CRP-POCT) management strategy resulted in a 20% reduction in patient-reported antibiotic consumption over four weeks following consultations for AECOPD in primary care.

Understanding the perceived value of CRP-POCT to clinicians and patients, potential mechanisms, and identifying barriers and facilitators to its use is vital in informing implementation plans.

Our study indicated that the CRP-POCT had high acceptability for use in the management of acute exacerbations of COPD in general practice, increasing clinician confidence, reducing decisional uncertainty, and as a tool to facilitate communication and patient education.

General Practitioners should consider adopting CRP-POCT in the routine management of acute exacerbations of COPD, but commissioning arrangements and further simplification of the point-of-care test need attention to facilitate this.

Abstract
Background: Antibiotics are prescribed to over 70% of patients presenting in primary care with an acute exacerbation of chronic obstructive pulmonary disease (AECOPD). The PACE randomised controlled trial found that a C-reactive protein point-of-care test (CRP-POCT) management strategy resulted in a 20% reduction in patient-reported antibiotic consumption over four weeks following consultations for AECOPD in primary care.
Aim: To understand perceptions of the value of CRP-POCT for guiding antibiotic prescribing for AECOPD; explore possible mechanisms, mediators, and pathways through which the intervention had its effects, and; identify potential barriers and facilitators to implementation from the perspectives of patients and clinicians.

Design and setting: Qualitative process evaluation in UK general practices.

Method: Semi-structured telephone interviews with 20 patients presenting with an AECOPD and 20 primary care staff, purposively sampled from the PACE study. Interviews were audio-recorded, transcribed, and analysed using framework analysis.

Results: Patients and clinicians felt that CRP-POCT was useful in guiding clinicians’ decisions about prescribing antibiotics for AECOPD, and were positive about introduction of the test in routine care. The CRP-POCT enhanced clinician confidence in antibiotic prescribing decisions, reduced decisional ambiguity, and facilitated communication with patients. Some clinicians thought the CRP-POCT should be routinely used in consultations for AECOPD, others favoured use only when there was decisional uncertainty. CRP-POCT cartridge preparation time and cost were potential barriers to implementation.

Conclusions: CRP-POCT guided antibiotic prescribing for AECOPD had high acceptability, but commissioning arrangements and further simplification of the point-of-care test need attention to facilitate implementation in routine practice.
Introduction

A multi-national study found that 79% of patients presenting in primary care with an acute exacerbation of chronic obstructive pulmonary disease (AECOPD) were prescribed an antibiotic, ranging from 49% of patients in Denmark to 93% of patients in Russia (1). However, antibiotics are unlikely to provide meaningful benefit for most outpatients with AECOPD (2). Unnecessary use of antibiotics increases the threat to society from antibiotic resistance, and increases individual patients’ risk of side-effects and carriage of resistant organisms in their lungs that may in turn increase risk of subsequent exacerbations and disease progression (3-6).

Current guidelines recommend using symptoms as the main guide to making antibiotic prescribing decisions for AECOPD (7, 8). C-reactive protein (CRP) is an acute phase reactant and raised levels are associated with AECOPD (1, 9). The PACE Study randomised 653 participants at 86 General Practices in the United Kingdom to establish whether CRP point-of-care testing (CRP-POCT) could safely reduce antibiotic consumption for AECOPD (10). The PACE study found that use of CRP-POCT and guidance on interpretation of the test in primary care led to a 20% reduction in the consumption of antibiotics over the four weeks following consultation for an AECOPD, without compromising recovery at two weeks post-consultation compared to usual care (11).

Process evaluations are an important part of evaluating complex interventions, providing a better understanding of the implementation and receipt of interventions and the context in which they were delivered (12, 13). This qualitative process
evaluation was embedded within the PACE study (10, 11) to better understand the acceptability of CRP-POCT guided antibiotic prescribing for AECOPD; explore possible mechanisms, mediators, and pathways through which the intervention had the effects observed in the quantitative component of the study (11), and; identify potential barriers and facilitators to implementation from the perspectives of patients and clinicians.

Method

Setting and participants

We used a purposeful sampling method using pre-defined criterion (14, 15) to select 20 patients in the CRP-POCT trial arm of the PACE Study, and 20 members of primary care teams who had carried out the CRP-POCT with patients or had used the CRP-POCT result during patient consultations to guide their prescribing decision (i.e. where the CRP-POCT had been carried out by another member of the primary care team). The sampling framework was designed to ensure representation from patients and primary care teams in each of the regions where the PACE study centres were located (Wales, Oxford, London and Norfolk), and from patients who had, and had not, been prescribed antibiotics at their initial consultation. Patients who had provided consent to be contacted about an interview at the start of the study were contacted by telephone.

As part of the PACE Study, primary care staff were provided with brief training in use of the CRP-POCT and guidance on interpretation and use of the CRP-POCT test result. The CRP-POCT was used in addition to usual best practice, with the test result being used to guide – but not mandate - antibiotic prescribing. The guidance stated that people with a CRP-POCT reading of <20 would probably not benefit from antibiotics, between 20 and 40 may benefit from antibiotics, and that antibiotics are likely to be
beneficial for those with a reading of >40. Full details are provided in the trial protocol (10).

The PACE study adopted a pragmatic approach to implementation of the CRP-POCT, allowing primary care practices to arrange for the test to be conducted in way that fitted with their own structure and processes (10). This meant that staff other than the doctor, including nurses, healthcare assistants, and research assistants with appropriate training sometimes undertook the CRP-POCT testing. We included some of these individuals in the interviews to see how the test was used in these different contexts.

The PACE Study was granted ethical approval by the Research Ethics Committee (REC) For Wales (Wales REC 6). Written informed consent was obtained from all patients. Primary care staff provided verbal consent, which was audio-recorded. Patient participants were sent a £10 gift voucher after their interview as a gesture of appreciation for their time. Primary care staff were not provided with incentives for participation in qualitative interviews, as they completed these as part of their wider involvement in the PACE Study research activities.

**Approach**

Flexible topic guides were used to guide interviews. The topic guides were piloted with patients (n=10) and primary care staff (n=9) and refined prior to use in this study. Interviews were audio-recorded and field notes were made. Transcripts were not returned to participants for comment and no repeat interviews were carried out. Interviews were carried out by experienced qualitative interviewers employed on the PACE study (HS, BSc, ASM, PhD). Their role as non-clinical researchers was explained to interview participants. Interviewers had no prior relationship with
participants. Researchers were provided with study specific training and supervision by an experienced qualitative researcher (RP, PhD).

**Analysis**

Interviews were transcribed verbatim. NVivo 11 qualitative analysis software was used to assist coding and facilitate analysis. Data were analysed using framework analysis, a systematic approach to a thematic analysis that allows for easy comparisons between and within cases, facilitates sharing and discussion of data, and allows for clear linking of developed themes to original data (16-18). The data were analysed using a hybrid inductive and deductive approach, based primarily on social phenomenology (19). The framework analysis (familiarisation, development of framework, and charting) took place before the trial outcomes were known, in line with the MRC guidance on process evaluation (12). HS carried out the data coding. Our protocol did not include dual coding of the data. Instead, we used regular qualitative research team meetings with the Trial Management Group at key junctures in the analysis to discuss data production, the development of the coding framework, and data analysis. This approach has been identified as appropriate in qualitative research (20). 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 (21). The qualitative researchers (RP & HS) assessed whether the last five interviews with primary care staff and patients provided new information that would add to the thematic framework being developed. On this basis, the judgement was made that data saturation had been achieved.
Results

Interview participant characteristics are shown in Table 1. Semi-structured interviews were conducted with 20 clinicians and other primary care staff that undertook CRP-POCT testing, across 19 practices. Of the 47 primary care practices that were invited to participate, two declined, two were unable to take part as they had not randomised any participants to the CRP-POCT arm, and 24 did not respond. Antibiotic prescribing rate were similar in practices who did (56.1%) and did not (60%) take part in the qualitative interviews.

Interviews were carried out with 20 patients across four centres (Wales, Oxford, London and Norfolk). Of the 40 patients invited to take part in an interview, 16 declined, one was in hospital when telephoned, and two were interested but unable to arrange a suitable time for an interview. A participant from the control arm of the trial was recruited for the interviews erroneously and their data was not included in this analysis. HS or ASM conducted one-to-one interviews between October 2015 and March 2017. A practice manager briefly joined the discussion part way through one interview with a clinician. Patient interviews lasted between 15 and 35 minutes; primary care staff interviews lasted between 20 and 45 minutes.

Framework analysis

Key themes identified through the framework analysis related to: 1) perceptions of the value of the CRP-POCT, 2) possible mechanisms of impact of the CRP-POCT, and 3) implementation of the CRP-POCT in routine practice. A summary of key findings is provided in Table 2.
1. Perceptions of the value of the CRP-POCT

While clinicians felt the CRP-POCT provided useful information, several felt this only affected their decision when there was uncertainty about whether antibiotics were needed. They emphasised the importance of using clinical findings to guide antibiotic prescribing decisions, and did not view the CRP-POCT as a replacement for clinical skills:

“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 1)

Clinicians talked about the added value of the test, as demonstrated by this clinician who described a case where a CRP reading had been unexpectedly high:

“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 1)
Primary care staff felt that the CRP-POCT reassured patients, and that the test demonstrated to patients 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 2)

Clinicians were aware of the need to reduce antibiotic prescribing, and felt that the perceived risk of under-treatment was a driver for prescribing unnecessary antibiotics 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 3)

The perception that early prescribing can reduce hospitalisation is at odds with evidence from a Cochrane review which did not find evidence that antibiotic prescribing for AECOPD in outpatient settings has an effect on hospital admissions or mortality. A GP also raised the issue of fear of litigation, where the CRP-POCT was seen as providing objective evidence to help justify prescribing decisions.

“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 5)

Patients felt the CRP-POCT could ‘help’ doctors with their decisions, and did not report any anxiety about having the test. Patients felt that the CRP-POCT was useful in rapidly deducing the severity of illness and/or 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”

(Patient 1, female, CRP <20, no antibiotics)

2. Perceived mechanisms of impact of the CRP-POCT

Three sub-themes were identified relating to perceptions about how the use of the CRP-POCT might achieve the desired aim of safely reducing antibiotic use: the CRP-POCT as an objective sign of illness; use of the CRP-POCT to enhance patient-clinician communication, and; use of the CRP-POCT to reinforce the prescriber’s decision.

The CRP-POCT provided an objective sign of illness severity

Prescribers reported that the CRP-POCT reading provided objective evidence 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 1)

Being able to share the reading with patients helped to provide objective evidence to provide support for treatment decisions when communicating with patients.

“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 4)

Clinicians felt that the CRP-POCT 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 way of reassuring me and the patient actually, it seemed to place a great deal of, you know, faith on, on blood testing”

(General Practitioner 5)

Many 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”

(Patient 2, female, CRP 20-40, prescribed antibiotics)
However, one patient viewed the CRP-POCT negatively as they 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 [I had] an ever [so] slight inflammation which they took because of this blood test she found and she gave me five days of the steroids, but after the five days I was back to square one.”

(Patient 3, male, CRP <20, no antibiotics)

The CRP-POCT enhanced physician-patient communication

Clinicians felt that patients had greater involvement in the consultation through discussion of the test outcome, and that it provided them with an opportunity to talk to patients about antibiotic stewardship:

“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 3)

From the patient perspective, there was a reasonable level of understanding of the purpose of the CRP-POCT in terms of guiding doctors’ antibiotic prescribing decisions.

“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”
Nonetheless, some patients were uncertain about what the CRP-POCT was testing, and there were some misconceptions about the type of infection that would require antibiotic treatment.

“They need to confirm, which is what I thought this test and that was doing, that it is, it is a proper viral infection”

(Patient 5, male, CRP 20-40, prescribed antibiotics)

**CRP-POCT reinforced prescribers’ decisions**

The CRP-POCT reading was generally used by clinicians to articulate and justify their prescribing 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)

Patients felt that their prescribers were, and should be, the decision-makers with regard to antibiotic treatment.

“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.”
Patients who perceived being involved in decision making about antibiotic prescription described this in terms of their agreeing with the doctor’s decision and having confidence in their expertise or because they felt that the doctors had explained their decision to them, rather than being actively involved in the decision-making process per sé.

“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”

(Patient 7, male, CRP<20, prescribed antibiotics)

3. Implementation of the CRP-POCT

Views about implementation in routine practice

Patients and primary care staff had a positive view about whether the CRP-POCT should be introduced into routine National Health Service (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 7)
Primary care staff discussed the advantages of using the test in routine care mainly in terms of antibiotic stewardship and achieving more consistent 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. From the patient perspective, their priority when they had an AECOPD was to resolve their symptoms. 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 weren’t 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”

(Patient 6, female, CRP<20, no antibiotics)

Within this context, they were receptive to the use of the CRP-POCT in routine care.

“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.”

(Patient 4, female, CRP<20, not prescribed antibiotics)

Clinicians and other primary care staff had mixed views on how the test should be implemented. Some clinicians felt that using the CRP-POCT for all patients presenting
with AECOPD to ‘increase their data’, provided a learning tool to improve their ability
to detect patients who need antibiotic treatment. Others felt they would only use the
CRP-POCT when there was decisional uncertainty about the need for antibiotics.

Technical aspects of the CRP-POCT

Patients did not report any difficulties with the use of the CRP-POCT by clinicians.
Primary care staff reported being able to use the CRP-POCT with all patients
randomised to the intervention arm, and in general the CRP-POCT was easy to use.
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 seen as
burdensome and were potential barriers to implementation. Clinicians felt that some
modifications to the technology would facilitate implementation.

“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 8)

“I think it would be nicer if it was, you know in and 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 7)

Time & resources
Patients felt that use of the test was quick. The primary care staff felt that using the CRP-POCT made consultations slightly longer, but felt that this was a good investment of their time:

“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 9)

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

Contextual factors that could influence the way the CRP-POCT is implemented

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. Patient anxiety, a strong patient preference for antibiotics, and individual circumstances (e.g. recent death of a spouse) were cited by primary care staff as reasons for still prescribing antibiotics despite a low CRP-POCT result, indicating that non-medical factors continued to influence antibiotic prescribing.

Discussion

Summary
We found that patients and clinicians considered CRP-POCT useful in guiding management of AECOPD by providing an indication of disease severity, facilitating communication with patients and managing their expectations, and increasing clinician and patient confidence in antibiotic prescribing decisions. Previous research identified difficulties with interpreting the implications of CRP results and concerns about distracting from clinical reasoning as perceived barriers to implementing CRP-POCTs (22). In the PACE study, clinicians were given guidance on the interpretation of the CRP-POCT result and were asked to use the CRP-POCT with all patients randomised to the CRP-POCT trial arm. Our clinician respondents did not report difficulties in interpreting the CRP-POCT or any negative impact on their clinical judgement. Likewise, our patient respondents felt the CRP-POCT was useful in guiding their doctors’ antibiotic prescribing decisions and felt that it would be acceptable for use in routine care.

**Strengths and limitations**

General practitioners and patients who agreed to participate in the trial may have more favourable views about this technology than those who did not agree to participate. Nonetheless, the interview participants were purposively sampled using a maximum variation approach to ensure that we captured a range of views, and our findings are therefore likely to be representative of those that would be willing to consider use of the test. Approximately 50% of practices and 40% of patients invited for interviews in the current study declined or did not respond, thus self-selection to the interviews may also have introduced a sampling bias. An implementation study involving a wider roll-
out of the intervention would be required to investigate to what extent the findings our study generalise to a broader population.

Comparison with existing literature

Patients with COPD are at risk of developing frequent and severe respiratory infections that can have a long-term impact on their lung function (23), and in this sense are a higher risk group than those presenting with uncomplicated acute cough presenting in primary care. Nonetheless, clinicians and patients in our study expressed similar views of the use of CRP-POCT to guide antibiotic prescribing as those that have been reported in studies of acute cough (22, 24-29). Potential benefits to using CRP-POCT routinely include improved opportunity for early intervention, reduced hospital admissions, and reducing unnecessary use of antibiotics by improving diagnostic confidence and improving communication with patients (24, 30, 31).

CRP-POCTs are widely used in a number of European countries in the management of LRTIs, but have not yet become routinely used in the UK (30). The absence of a funding and reimbursement model has been identified as the primary barrier for widespread adoption of the CRP-POCT for acute cough in the NHS (30). This concern was shared by the clinicians we interviewed in the PACE study and should be addressed by commissioners and policy makers to enable implementation of the CRP-POCT in routine care for AECOPD.
Previous research has suggested that risk aversion and the perception that the CRP-POCT time consuming are potential barriers to its adoption (30). In our study, clinicians felt that the CRP-POCT would reduce risk to patients through better targeting of antibiotics, and as such the time invested in carrying out the test was worthwhile. In European countries where CRP-POCT is routinely used for acute cough, typical patient pathways for CRP-POCT include GPs or practice nurses carrying out the CRP-POCT during their consultations with patients (30). Other appropriately trained members of primary care teams can complete the CRP-POCT and pass the information on to prescribing clinicians (30). In the PACE study, practices could use any of these options to enable them to adapt the implementation of the CRP-POCT to fit with their practice routines (10). Clinicians had mixed views on how the CRP-POCT should be implemented in terms of whether it should be used with all patients, or only in cases where there was clinical uncertainty. Guidance for clinicians will be required in introducing CRP-POCT in routine practice for AECOPD to facilitate its implementation in a consistent and effective way.

The PACE trial found reduced antibiotic prescribing for AECOPD from CRP-POCT use. Nevertheless, antibiotics were prescribed for 33% of patients who had a CRP-POCT level of <20mg, where guidance indicated that antibiotics were unlikely to be of benefit (11). Non-clinical contextual factors, such patient expectations for antibiotics, access to antibiotics before consulting with a clinician, and a lack of clear guidelines can influence clinicians’ antibiotic prescribing behaviour for acute cough (32). Being able to effectively elicit patient ideas, concerns, expectations, and beliefs is an important skill for clinicians managing acute cough (27, 33, 34). There was a perception amongst some patients that the CRP-POCT provided an accurate indication
on ‘how ill’ they were, as well some misconceptions around the necessity of antibiotics for bacterial and viral infections. Providing patients with more information about the function of the test and effective management of exacerbations may therefore be of benefit. In acute cough, a combination of training use of a CRP-POCT and enhanced communication-skills training has a larger effect than either form of training alone (34). Additional training for clinicians in integrating the CRP-POCT into consultations in a patient-centred way and enhanced information for patients about the purpose and potential benefits of testing might facilitate adoption.

**Implications for practice**

Patients and clinicians reported that the CRP-POCT led to less clinical uncertainty, increased prescribing confidence, and enhanced communication. These were all potential mechanisms for a safe reduction in overall antibiotic use for AECOPD. Both patients and clinicians emphasised the need to use the CRP-POCT as part of, not in place of a high-quality consultation that includes a clinical examination, elicitation of patient views and preferences, the application of the prescriber’s clinical judgement, and information on how and when patients should re-consult if they are not recovering as expected. Taken together with the quantitative findings from our trial (11), the findings of this study suggest that practitioners should consider adopting CRP-POCT in the routine management of AECOPD. Implementation planning for the CRP-POCT should include consideration of funding arrangements, simplifying the CRP-POCT technology so that it is quicker and easier to use, guidelines on implementation of the test for clinicians, and better information for patients.

**Additional Information**
Funding: The PACE study was funded by the NIHR Health Technology Assessment Program (project number 12/33/12). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. The work was undertaken with the support of the UK Clinical Research Collaboration (UKCRC) registered Centre for Trials Research, who receive infrastructure funding from Health and Care Research Wales and Cancer Research UK, and the UK Clinical Research Collaboration (UKCRC) registered University of Oxford Primary Care and Vaccines Clinical Trials Consortium. Neither the NIHR nor Health and Care Research Wales had a role in study design, data collection, data analysis, data interpretation, and report writing.

Ethical approval: The PACE Study protocol was approved on 15 September 2014 by the Research Ethics Committee (REC) For Wales (Wales REC 6) recognized by the United Kingdom Ethics Committee Authority (REC reference: 14/WA/1106). Written informed consent was obtained from all patients who took part in an interview. Primary care staff offered their consent to take part in the interview verbally over the telephone.

Acknowledgements: We would like to thank all of those who have supported the PACE study, including the members of the PACE study research team, Trial Management Group, Trial Steering Committee, and Independent Data Monitoring and Ethics Committee, as well as the patients and primary health care staff who took part in these interviews for their time and for sharing their views with us. We would also like to acknowledge and thank the Health and Care Research Wales Workforce; the Thames Valley and South Midlands, Eastern, and West of England Primary Care
Research Networks (PCRNs), and: Comprehensive Local Clinical Research Networks (CLRNs) for their support in recruiting sites for the PACE study.

Conflict of interest: RP and MG were Research Fellows at the Wales Centre for Primary and Emergency Research, Cardiff University, supported by a Research Centre Grant from Health and Care Research Wales during the completion of this study. CCB is a 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 Cooperative. He has received fees from Roche Diagnostics for participating in an Advisory Board about point of care testing; holds a grant from Roche Diagnostics to evaluate the analytic performance of a point of care testing device, and; is part of publicly funded research consortia that include industrial partners. JC is professor and primary care physician at the department of Family Medicine at Maastricht University. He is supported by a Veni-grant (91614078), of the Netherlands Organization for Health Research and Development (ZonMw). KH is a HCRW Senior Investigator and Director of the Centre for Trials Research.

References

1. Llor C, Bjerrum L, Munck A, et al. Predictors for antibiotic prescribing in patients with exacerbations of COPD in General Practice. Ther Adv Respir Dis. 2013. doi:10.1177/1753465812472387
2. Vollenweider DJ, Jarrett H, Steurer-Stey CA, et al. Antibiotics for exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2012;12:Cd010257. doi:10.1002/14651858.cd010257

3. Soler N, Ewig S, Torres A, et al. Airway inflammation and bronchial microbial patterns in patients with stable chronic obstructive pulmonary disease. Eur Respir J. 1999;14(5):1015-22.

4. Cosby JL, Francis N, Butler CC. The role of evidence in the decline of antibiotic use for common respiratory. Lancet Infect Dis. 2007;7(11):749-56. doi:10.1016/s1473-3099(07)70263-3

5. Costelloe C, Metcalfe C, Lovering A, et al. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. BMJ. 2010;340:c2096. doi:10.1136/bmj.c2096

6. Goossens H, Ferech M, Vander Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. Lancet. 2005;365(9459):579-87. doi:10.1016/s0140-6736(05)17907-0

7. Global Initiative for Chronic Obstructive Lung Disease (GOLD). GOLD 2017 global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease 2017.

8. National Institute for Health and Care Excellence. Clinical guideline 101. Chronic obstructive pulmonary disease in over 16s: diagnosis and management. United Kingdom 2010.

9. Hurst JR, Donaldson GC, Perera WR, et al. Use of plasma biomarkers at exacerbation of chronic obstructive pulmonary. Am J Respir Crit Care Med. 2006;174(8):867-74. doi:10.1164/rccm.200604-506OC
10. Bates J, Francis NA, White P, et al. General practitioner use of a C-reactive protein point-of-care test to help target antibiotic prescribing in patients with acute exacerbations of chronic obstructive pulmonary disease (the PACE study): study protocol for a randomised controlled trial. Trials. 2017;18(1):442. doi:10.1186/s13063-017-2144-8

11. Butler CC, Gillespie D, White P, et al. C-Reactive Protein Testing to Guide Antibiotic Prescribing for COPD Exacerbations. New Engl J Med. 2019;381(2):111-20. doi:10.1056/NEJMoa1803185

12. Moore G, Audrey S, Barker M, et al. Process evaluation of complex interventions: Medical Research Council guidance. BMJ. 2015;350. doi:10.1136/bmj.h1258

13. Oakley A, Strange V, Bonell C, et al. Health services research: process evaluation in randomised controlled trials of complex interventions. BMJ. 2006;332(7538):413.

14. Cresswell J, Plano Clark V. Designing and conducting mixed method research. 2nd Sage. Thousand Oaks, CA. 2011;201.

15. Palinkas LA, Horwitz SM, Green CA, et al. Purposeful Sampling for Qualitative Data Collection and Analysis in Mixed Method Implementation Research. Adm Policy Ment Health. 2015;42(5):533-44. doi:10.1007/s10488-013-0528-y

16. Gale N, Heath G, Cameron E, et al. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. BMC Med Res Methodol. 2013;13(117).

17. Srivastava A, Thomson SB. Framework analysis: a qualitative methodology for applied policy research. Journal of Administration and Governance. 2009;4(2):72-8.
18. Ritchie J, Spencer L. Qualitative data analysis for applied policy research. In: Bryman A, Burgess R, editors. Analyzing Qualitative Data. London: Routledge; 1994.

19. Fereday J, Muir-Cochrane E. Demonstrating Rigor Using Thematic Analysis: A Hybrid Approach of Inductive and Deductive Coding and Theme Development. Int J Qual Methods. 2006;5(1):80-92. doi:10.1177/160940690600500107

20. Barbour RS. Checklists for improving rigour in qualitative research: a case of the tail wagging the dog? BMJ. 2001;322(7294):1115-7. doi:10.1136/bmj.322.7294.1115

21. Fusch P, Ness L. Are we there yet? Data saturation in qualitative research. Qual Rep. 2015;20(9):1408-16.

22. Wood F, Brookes-Howell L, Hood K, et al. A multi-country qualitative study of clinicians' and patients' views on point of care tests for lower respiratory tract infection. Family Practice. 2011;28(6):661-9. doi:10.1093/fampra/cmr031

23. Sethi S. Infection as a comorbidity of COPD. Eur Respir J. 2010;35(6):1209-15. doi:10.1183/09031936.00081409

24. Cals JWL, Chappin FHF, Hopstaken RM, et al. C-reactive protein point-of-care testing for lower respiratory tract infections: a qualitative evaluation of experiences by GPs. Fam Pract. 2010;27(2):212-8. doi:10.1093/fampra/cmp088

25. Hardy V, Thompson M, Keppel GA, et al. Qualitative study of primary care clinicians' views on point-of-care testing for C-reactive protein for acute respiratory tract infections in family medicine. BMJ Open. 2017;7(1). doi:10.1136/bmjopen-2016-012503

26. Anthierens S, Tonkin-Crine S, Cals JW, et al. Clinicians' Views and Experiences of Interventions to Enhance the Quality of Antibiotic Prescribing for
27. Tonkin-Crine S, Anthierens S, Francis NA, et al. Exploring patients' views of primary care consultations with contrasting interventions for acute cough: a six-country European qualitative study. NPJ Prim Care Respir Med. 2014;24:14026. doi:10.1038/npjpcrm.2014.26

28. Cals JW, Butler CC, Dinant G-J. 'Experience talks': physician prioritisation of contrasting interventions to optimise management of acute cough in general practice. Implement Sci. 2009;4(1):57. doi:10.1186/1748-5908-4-57

29. Tonkin-Crine S, Anthierens S, Francis NA, et al. Exploring patients' views of primary care consultations with contrasting interventions for acute cough: a six-country European qualitative study. NPJ Prim Care Respir Med. 2014;24. doi:10.1038/npjpcrm.2014.26

30. Huddy JR, Ni MZ, Barlow J, et al. Point-of-care C reactive protein for the diagnosis of lower respiratory tract infection in NHS primary care: a qualitative study of barriers and facilitators to adoption. BMJ Open. 2016;6(3). doi:10.1136/bmjopen-2015-009959

31. Anthierens S, Tonkin-Crine S, Douglas E, et al. General practitioners' views on the acceptability and applicability of a web-based intervention to reduce antibiotic prescribing for acute cough in multiple European countries: a qualitative study prior to a randomised trial. BMC Fam Pract. 2012;13. doi:10.1186/1471-2296-13-101

32. Brookes-Howell L, Hood K, Cooper L, et al. Clinical influences on antibiotic prescribing decisions for lower respiratory tract infection: a nine country qualitative study of variation in care. BMJ Open. 2012;2(3). doi:10.1136/bmjopen-2011-000795
33. Coenen S, Francis N, Kelly M, et al. Are patient views about antibiotics related to clinician perceptions, management and outcome? A multi-country study in outpatients with acute cough. PloS one. 2013;8(10):e76691. doi:10.1371/journal.pone.0076691

34. Little P, Stuart B, Francis N, et al. Effects of internet-based training on antibiotic prescribing rates for acute respiratory-tract infections: a multinational, cluster, randomised, factorial, controlled trial. Lancet. 2013;382(9899):1175-82. doi:10.1016/s0140-6736(13)60994-0
Table 1: Characteristics of qualitative process evaluation participants

| Patients                      | N | Prescribed antibiotics at index consultation (n) | Not prescribed antibiotics at index consultation (n) |
|-------------------------------|---|-------------------------------------------------|-----------------------------------------------------|
| CRP reading <20               | 14| 4                                               | 10                                                  |
| CRP reading >20               | 6 | 5                                               | 1                                                   |
| Total patients                | 20| 9                                               | 11                                                  |

| Primary care staff            | N | Made prescribing decisions guided by CRP-POCT result (n) | Carried out the CRP-POCT (n) |
|-------------------------------|---|-------------------------------------------------|----------------------------|
| General Practitioners         | 12| 12                                              | 7                          |
| Nurse Practitioners           | 5 | 5                                               | 5                          |
| Non-prescribers               |   |                                                 |                           |
| Practice nurse                | 1 | 0                                               | 1                          |
| Research assistant            | 1 | 0                                               | 1                          |
| Pharmacist                    | 1 | 0                                               | 1                          |
| Total primary care staff      | 20| 17                                              | 15                         |
| Main theme | Sub-theme | Patient views | Primary care staff views |
|------------|-----------|---------------|-------------------------|
| Perception of the value of the CRP-POCT | General views of the CRP-POCT | Many felt that the CRP-POCT was a useful addition to the consultation that would help guide their doctor’s antibiotic prescribing decision. | Most thought the CRP-POCT was a useful addition to the consultation, particularly where there was diagnostic uncertainty. Clinicians emphasised the importance of using the CRP-POCT in addition to, not in place of, a thorough clinical assessment. |
| Perceived mechanisms of impact of the CRP-POCT | Objective sign of illness | Patients felt that the CRP-POCT provided an objective sign of illness severity that could help guide treatment. | Prescribers felt that having this additional piece of objective evidence increased their confidence in their antibiotic prescribing decisions. |
| | Enhancing patient-clinician communication | CRP-POCT useful in understanding whether antibiotics are needed, but some misconceptions about when antibiotics might or might not be helpful (e.g. for viral infections). | Primary care staff felt that the test provided an opportunity to open discussions with patients about antibiotic use and antimicrobial resistance. |
| | Reinforcing prescribers’ decisions | Patients were generally passive in terms of making decisions about antibiotic treatment, with clinicians explaining their decision to/not to prescribe antibiotics to them. | Primary care staff perceived the CRP-POCT result as being useful in reinforcing their decision about antibiotic prescribing when communicating with patients. |
| Implementation of the CRP-POCT | Views about implementation in routine practice | Many patients expressed positive attitudes towards the use of the CRP-POCT in routine NHS care for the management of AECOPD. | Positive attitudes towards the use of the CRP-POCT in routine NHS care, but there were differences of opinion about whether the CRP-POCT would be used for all patients with AECOPD, or only those where there was clinical uncertainty. |
| | Technical aspects of the test | Patients did not report any difficulties with the use of the CRP-POCT by clinicians. | Found the CRP-POCT easy to use, but felt that the need for test cartridges to be refrigerated during storage and returned to room temperature before use, need for regular calibration of the machine, and lack of portability of the device were potential barriers to widespread use in primary care. |
| | Time & resources | Patients felt that use of the test was quick, didn’t report any problems with administration of the test. | Acknowledged the impact on consultation length that use of the CRP-POCT had, but felt that it was worthwhile. Felt that the cost of the CRP-POCT machine and cartridges was prohibitive under current funding arrangements. |
| Contextual factors | Non-medical factors that influenced prescribing | 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. | Patient anxiety, a strong patient preference for antibiotics, and individual circumstances (e.g. recent death of a spouse) were cited by primary care staff as reasons for still prescribing antibiotics despite a low CRP-POCT result. |