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Targeted case finding for COPD *versus* routine practice in primary care (TargetCOPD): a cluster randomised controlled trial

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RESEARCH IN CONTEXT

Evidence before this study

It is widely accepted that COPD is substantially under-diagnosed worldwide. Mass population screening with spirometry is not recommended although early identification of undiagnosed patients with clinical disease is generally supported because COPD has significant patient, healthcare and societal burden which could potentially be lessened through timely diagnosis. A comprehensive systematic review of the effectiveness of case-finding studies, published in 2015, revealed 39 published studies but few included a comparator arm. Only one RCT has compared a case-finding approach with routine care to identify clinically significant COPD, identifying that opportunistic administration of a screening questionnaire at practice visits was twice as effective as routine care, but non-comparative studies suggest that high yields could be achieved from active case finding with mailed questionnaires to high risk patients. No previous trial has compared the clinical and cost-effectiveness of alternative approaches to case-finding in a real-life primary care setting.

Added value of this study

TargetCOPD is the first randomised controlled trial to evaluate the effectiveness and cost-effectiveness of active case-finding for COPD compared with opportunistic case finding and to compare these approaches with routine care. Among 54 general practices, we found that when targeting ever smokers aged 40-79 years, active case finding was more than twice as effective as opportunistic case finding, and that together, these targeted approaches were over seven times as effective as current routine care. Active case finding was also more cost-effective than opportunistic case finding.

Implications of all the available evidence

In a real-life setting, active case-finding comprising an initial mailed questionnaire followed by spirometry should be recommended for identifying undiagnosed COPD in primary care. An important proportion of these previously undiagnosed patients have significant breathlessness and earlier identification and management with effective treatments including inhalers and pulmonary rehabilitation has the potential to improve their health. This trial provides the evidence for guidelines which was previously lacking.

SUMMARY

Background

Many individuals with chronic obstructive pulmonary disease (COPD) remain undiagnosed worldwide. Healthcare organisations are implementing case-finding programmes without good evidence of which are the most effective and cost-effective approaches.

Methods

This cluster randomised controlled trial (RCT) among general practices in the West Midlands, UK, compared the effectiveness and cost-effectiveness of two alternative approaches to targeted case finding with routine practice among ever-smokers aged 40-79 years without a prior recorded diagnosis of COPD. Patients in targeted practices were randomised *via* their households to receive screening questionnaires at GP consultations (opportunistic) or additionally by mail (active) and compared with the routine care arm. Respondents reporting relevant respiratory symptoms were invited for post-bronchodilator spirometry. Primary outcomes at 12 months among all eligible participants were probability of detecting a new case of COPD for each treatment arm and cost per new COPD diagnosis (defined as post-bronchodilator FEV1/FVC<0.7 among patients with symptoms or a new diagnosis on their GP record). Multiple logistic and Poisson regression were used to estimate effect sizes. Costs were obtained from the trial. This trial is registered as an International Standard Randomised Controlled Trial, number ISRCTN14930255.

Findings

54 diverse general practices (74,818 eligible patients) were randomised and completed the trial (August 2012-June 2014). Overall 1278/32,789 (3.9%) cases were newly detected in the targeted arm compared with 337/42,029 (0.8%) in the routine practice arm, adjusted OR 7.45 (95%CI 4.80, 11.55)(p<0.001). Active case-finding was more effective than opportunistic (adjusted OR 2.34 (2.06, 2.66)(p<0.001), adjusted risk difference 2.9 per 100 patients (95%CI 2.3, 3.6)), and more cost–effective (£333 *vs* £376 per case detected).

Interpretation

In this well-established primary care system, routine practice identified few new cases. An active targeted approach including mailed screening questionnaires prior to spirometry is a cost-effective way to identify undiagnosed patients and has the potential to improve their health.

Funding: National Institute for Health Research

Key words: COPD; case-finding; screening; primary care; respiratory questionnaire; spirometry; cluster RCT; effectiveness; cost-effectiveness

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common long-term respiratory condition with high healthcare and societal burden[1] with estimated annual costs of $50 billion (2010) to the US[1] and €48.6 billion (2011) to the EU economy[2]. Worldwide, the diagnosed prevalence is estimated to be about 5% of adults over 40 years,[3] but at least an equivalent number with significant symptomatic COPD remain undiagnosed and could potentially benefit from effective interventions.[4-5] There is a worldwide drive to identify these "missing millions"[6-9] and many healthcare organisations are implementing case-finding programmes, although without good evidence of which are the most effective and cost-effective approaches.

There are numerous reports of uncontrolled studies of case-finding, with heterogeneous populations, interventions and case definitions.[10] However, only one published RCT, within family medical practices in the US, has evaluated a systematic approach to identifying previously undiagnosed clinical COPD compared with usual care.[11] This demonstrated that initial opportunistic administration of a screening questionnaire was twice as effective as usual care in identifying new cases of COPD. Other uncontrolled studies have suggested that sending a screening questionnaire by post prior to spirometry assessment is a promising alternative method,[10] but the comparative effectiveness and cost-effectiveness of the two approaches has not been tested.

Modelling of observational data suggested that an active approach (including both mailed questionnaires and opportunistic administration) could be twice as effective as an opportunistic-only approach, and identify patients with significant potential to benefit.[4] Here we present the findings from a large pragmatic cluster RCT in a UK primary care setting, to evaluate fully the effectiveness and cost-effectiveness of these two methods of identifying undiagnosed COPD.

METHODS

Study design

TargetCOPD was a pragmatic cluster RCT comparing an active and an opportunistic targeted approach to case finding for undiagnosed COPD with routine practice in primary care (Figure 1).[12] UK ethical and research governance approvals were obtained (Ref:11/WM/0403).

Practice and participant recruitment

All 354 general practices (GPs) (family medical practices) in the Birmingham and Black Country region of the West Midlands, UK were invited to take part. Automated computer searches of electronic health records (EHR)(Appendix 1) identified ever smokers aged 40 to 79 years without a prior diagnosis of COPD. Physicians then excluded at their discretion those they considered unsuitable (for example those unable to give informed consent, having terminal illness, being pregnant). The remaining patients were classed as "approved" to receive a screening questionnaire.

Randomisation and masking

General practices were initially randomised in three phases using variable block size by the trial statistician into targeted case finding or routine practice. Cluster randomisation was preferred so that healthcare staff in the routine care arm did not change their usual practice for control patients because of raised awareness about case finding, and because we wanted to assess a whole practice organisational approach which could be undertaken in "real-life". A published algorithm for cluster randomised trials was used to balance key practice characteristics (deprivation (Index of Multiple Deprivation score of the practice), ethnicity (%white patients), practice list size, age (% aged $\geq$ 45 years) and proportion of patients on the COPD register[13]) with stratification for linked practices. [12,14] Practices were unaware of their allocation until baseline patient data had been provided and they had agreed to commence the study. Within the targeted arm, individual households were subjected to block randomisation (block size 20) using a random number generator (automatically applied when participants from each practice were uploaded to the trial database) to active or opportunistic case finding, ensuring that patients from the same household were allocated the same intervention to avoid contamination. The allocation ratio was 1:1 for randomisation of both general practice and households. Data processing was computerised and research assistants carrying out spirometry assessments were unaware of the allocation.

Interventions

The case-finding intervention was applied for 12 months in each practice, with a staggered start (August 2012 – June 2013). 12 practices (6 targeted, 6 routine) formed an internal pilot phase to test procedures.

Targeted case finding arm

Eligible patients were allocated to receive a brief screening questionnaire (Appendix 2) in either of two ways:

(a) Opportunistic: patients' electronic health records (EHR) were flagged to prompt handing out the questionnaire during any visit to their general medical practice.

(b) Active: In addition to opportunistic distribution, the screening questionnaire was mailed to patients' homes (with reply-paid envelope). Reminders were sent after 4 and 8 weeks.

EHR prompts were removed after receipt of the questionnaire. All participants in the targeted arm were provided with patient information leaflets and a standard letter of invitation from their GP and respondents were considered to have implied consent by returning their questionnaire with their personal details.

The questionnaire was piloted by our patient advisory group.

Routine practice arm

The GPs in the routine practice arm were expected to follow UK guidance which recommends that patients aged >35 years should be investigated for COPD with spirometry if they present with chronic cough or phlegm, exertional breathlessness or wheeze.[15] National QOF data show that >80% of patients newly diagnosed with COPD receive confirmatory spirometry within 12 months.[13] Consent was not required from patients in the routine care arm as we did not obtain patient-identifiable data.

Spirometry diagnostic assessments

Patients in the targeted arm who responded to the screening questionnaire and reported any of the following respiratory symptoms (chronic cough/phlegm for $\geq$3 months for at least 2 years, wheeze in the last 12 months or dyspnoea of MRC grade 2 or more) were invited to attend their GP practice for confirmatory spirometry. Attendees provided signed informed consent at the start of the assessment. Post-bronchodilator spirometry was undertaken according to ATS/ERS 2005 guidelines[16] using an ultrasonic flow head (Spiroson-AS, ndd, Zurich) with bespoke software (MRMiller) and carried out by blinded, trained research assistants with immediate visual quality control monitoring and feedback. Every trace was over-read and quality of blows graded according to standard criteria.[17] Patients also completed a short questionnaire to ascertain out of pocket expenses for attendance (Appendix 3) and health status (EQ-5D).[18] Patients' height was measured to the nearest cm using a portable stadiometer (or estimated using arm-span if necessary).

Outcomes

Primary outcomes were the percentage of the eligible population diagnosed with COPD within one year, and cost per additional case identified in each arm, comparing (1) active and opportunistic case finding, then (2) targeted case finding and routine care. Secondary outcomes were feasibility (process

measures including uptake and resource needs) and efficiency (number needed to target to identify one person likely to benefit).

Diagnosing COPD

New cases in the targeted arm were identified either through the trial spirometry assessment visit (post-bronchodilator $FEV_1/FVC<0.7$ in the presence of respiratory symptoms, in line with recommended UK guidelines[15]) or through the EHR using automated searches with clinical (Read) codes (Appendix 1), to ensure fair comparison with the routine arm. New cases in the routine arm were identified from the EHR only as they did not receive a trial spirometry assessment. In sensitivity analyses we used the "Lower Limit of Normal" (LLN) definition (GLI 2012 equations[19]) to define airflow limitation.

Additional data collection

Additional data from the EHR were collected at baseline and 12 months to ascertain patient characteristics, medical conditions and study outcomes. In order to estimate opportunistic questionnaire distribution in the targeted arm, 30 patients from each of the opportunistic and active arms in each practice were randomly sampled to ascertain whether EHR prompts had been removed.

Sample size

The significance level for multiple testing was adjusted to provide a total of 5% significance level across the two primary effectiveness outcomes: 0.25% for the opportunistic *vs* active comparison, and 4.75% for the targeted *vs* routine care comparison. The sample size calculation was computed from estimates presented in our published model of case finding[4], which used data from the Health Survey for England and published literature to estimate values for different stages of the process, and provided in detail in our protocol.[12]

For the opportunistic *vs* active comparison, we assumed 50% allocated to the active arm would respond; of the remaining patients 91% would visit their GP at least once in 12 months, 50% would be offered the questionnaire and 90% of these would fill it out. In the Opportunistic arm we assumed 50% would be offered the questionnaire and of these 90% would complete questionnaires. Of all responders to the questionnaire in both arms, we assumed 48% would report symptoms and be invited to spirometry, of whom 70% would attend and 17% of these would have COPD. This would lead to yields of 2.3% in the opportunistic and 4.0% in the active arms. At a 0.25% significance level, 3904 patients/arm were required to detect this difference with 90% power.

For the targeted *vs* routine care comparison, the proportion of new COPD cases detected in the targeted group (averaged across both active and opportunistic arms) was assumed to be 3.15%. The proportion of new COPD cases detected in the routine care group was assumed to be 0.75%. At the

4.75% significance level, with 80% power, this led to an unadjusted sample size required of 545 per group, in order to detect a difference of 2.4% between targeted and routine care arms. We expected ~40% of a practice population to be aged 40-79yrs with 57% of these being ever smokers without a previous diagnosis of COPD. Assuming therefore a conservative 1000 eligible patients per practice of average list size 6000, and adjusting for clustering of patients within practices, assuming a conservative ICC of 0.05 the sample size required was 27,768 per arm, equivalent to 28 practices per arm.

Statistical analyses

All analyses were undertaken in Stata 13 (StataCorp LP, Texas). The process measures such as questionnaire response rates were presented using simple descriptive statistics. For the primary outcomes, all models used outcomes for individual participants and were adjusted for practice level deprivation (IMD – index of multiple deprivation), patient ethnicity and age, as pre-defined in the protocol.[12]

To compare opportunistic and active arms, logistic regression was used including a fixed effect for each practice (adjustment for household made little difference to results therefore was not presented). Adjusted relative risks and risk differences were also estimated using Poisson regression with robust standard errors,[20] and from these, numbers needed to target (NNT) were computed. The analysed population included only those patients approved by their GP to receive a screening questionnaire.

To compare targeted and routine care, the same approach was taken but multilevel regression models were used (logistic and Poisson with robust standard errors) with a separate random effect for targeted and routine practices, to allow for clustering and between-practice heterogeneity in the underlying log odds of COPD case-detection for each arm. In this case, the analysed population included all eligible patients meeting the entry criteria. An estimate of the ICC was obtained by fitting a multilevel linear null model.

Economic analyses

The base-case analysis estimated the cost per additional case detected with active and opportunistic case-finding compared with routine care, taking a healthcare perspective and using multi-level modelling in line with the main trial analysis.[12] Incremental cost-effectiveness ratios were calculated, by dividing the difference in mean per patient costs by the difference in mean patient outcomes (cases detected). A bottom-up approach was employed to cost the case-finding strategies, using data collected within the trial (Table 1). Standard NHS unit costs and trial-specific costs were applied to calculate the costs of each process (Appendix 4) using 2013 prices. Spirometry costs were calculated assuming that it would be provided by an NHS outreach service. Reusable equipment was amortised over five-years, and training costs spread over three years, using a discount rate of 3.5%, Costs incurred by patients and their families to attend spirometry assessments (including travel, care and

cost of time off work) were included in a sensitivity analysis and obtained by patient self-report while attending the assessment. Time spent away from paid work was valued at the average national wage rate. Costs incurred after COPD was confirmed were not considered in this analysis. Sensitivity analyses were also undertaken to estimate the cost-effectiveness of different models of care and alternative case-finding scenarios. Three alternative models of care were considered including a GP-led model, a community-led model and a secondary-care model (Appendix 4).

This trial is registered as an International Standard Randomised Controlled Trial, number ISRCTN14930255.

Role of the funding source

The funder had no role in study design, data collection, data interpretation, or writing of the report. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

56 GP practices agreed to participate (fig S1), but two withdrew before randomisation. Practices took part between August 2012 and June 2014. No practices were lost-to-follow-up by one year. Practice and participant characteristics were well balanced between targeted case finding and routine care (Table 2) although the routine arm (n=42,029 patients) was larger than the targeted arm (n=32,811) with some slight differences in distribution of smoking status and participants living in shared households. Practice characteristics were broadly representative of those in the Birmingham and Black Country region with a wide range of socioeconomic deprivation, practice size and populations served.

Targeted arm: opportunistic *vs* active case finding nested study

For the nested trial within the targeted arm, comparing opportunistic with active case finding, of a total of 32,811 patients, 30,787 were approved to be allocated a screening questionnaire by GPs. 15,393 were allocated to the opportunistic, and 15,394 to the active arm (figure S2), and 22 formally withdrew from the trial. Patient characteristics were similar between arms (Table S1). Values used below are for those analysed, excluding those withdrawing use of their data.

In the opportunistic arm, 89% (13718/15387) of patients consulted their GP/primary care professional within the 12 month period (see figure 1). Sampling of record-flags across practices suggested that screening questionnaires were distributed to 48.5% (95%CI 45.0, 52.0) of eligible patients in the opportunistic arm (range 0% to 100%). All eligible patients in the active arm received a questionnaire.

In the opportunistic arm, 1973/15387 (12.8% of eligible patients) returned their questionnaire (range 0-30.8%). In the active arm, 5808/15387 (37.8%) returned screening questionnaires, the majority (5042/15387, 86.8% of the total) after receiving it through the post rather than at the medical practice. Responses increased following each reminder; (2312/15378 (13.7%) after the initial invite, 1624/15378 (10.6%) after the first and 1086/15378 (6.7%) after the second reminder), and varied by GP practice (range 22.3% to 53.5%)(Table S2).

Among responders to the screening questionnaire, 4341/7781 (55.8%) reported symptoms triggering an invitation for spirometry assessment (opportunistic arm; 3264/5808 54.6%, active arm: 1077/1973 56.2%). 3142/7781 (40.4%) reported dyspnoea of MRC Grade 2 or worse, 2989/7781 (38.4%) wheeze in the past 12 months, 926/7781 (11.9%) chronic cough and 727/7781 (9.3%) chronic phlegm (Table S3). Chronic cough (752/5808 13.0% vs 174/1973 8.8%) and chronic phlegm (589/5808 10.1% vs 138/1973 7.0%) were more commonly reported in the active arm, although the prevalence

of dyspnoea and wheeze was similar in both arms. Non-responders were more likely to be younger, current smokers and of non-White British ethnicity than respondents.

543/1077 (50.4%) participants with respiratory symptoms in the opportunistic, and 2065/3264 (63.3%) in the active arm attended a spirometry assessment (figure S2). 93.8% of blows met Grade A-C quality criteria.[17] 851/2608 (32.6%) of assessed patients had airflow obstruction using the FEV1/FVC<0.7 criteria, and 529/2608 (20.3%) using GLI equations.

After one year, a larger percentage of new COPD cases were detected in the active (822/15387; 5.4%) compared with the opportunistic arm (n=370/15378; 2.4%), giving an adjusted OR of 2.34 (95%CI 2.06, 2.66)(p<0.001) and, assuming a baseline risk of 2.4%, an adjusted risk difference of 2.9 per 100 patients (95%CI 2.3, 3.6)(table 3). This effect varied across practices (figure S3) although all but one had an OR estimate in favour of the active group. 35 (95% CI 27.8, 43.5) screening questionnaires would need to be mailed to identify one extra COPD patient.

Among newly identified patients, severity of airflow obstruction was similar in both arms (table 3), with 819/851 (96.2%) classified as either mild (459/851; 53.9%) or moderate (360/851; 42.3%). 231/851 (27.1%) reported dyspnoea of MRC grade 3 or more, and 300/851 (35.3%) were current smokers.

In sensitivity analyses using GLI equations, 607/15378 (3.9%) and 303/15387 (2.0%) of the targeted population had undiagnosed COPD identified in the active and opportunistic arms respectively (adjusted OR 2.07 (1.80, 2.38)(p<0.001).

Targeted case finding *vs* routine care

In the routine arm, 337/42029 new cases of COPD were diagnosed after one year (0.8% of eligible patients) (Table 4) and considering all eligible patients (even if not approved for receiving a trial screening questionnaire), a total of 1278/32789 (3.9%) in the targeted arm. After adjusting for age, IMD score, ethnicity and clustering of practices (ICC=0.02), the likelihood of detecting undiagnosed COPD was much greater in the targeted arm (adjusted OR 7.45 (95%CI 4.80, 11.55), p<0.001). With a baseline risk of 0.8%, the adjusted risk difference was 4.9 per 100 patients (3.0, 7.7)) and therefore 21 (13.0, 33.3) patients would require targeting with a screening questionnaire (NNT) to identify one new case.

Sensitivity analyses using the lower limit of normal definition of COPD with GLI equations[19] attenuated the effect in the targeted arm (996/32789 new cases; 3.0% yield), although the approach remained significantly better than for the routine arm: adjusted OR=5.41 (3.47, 8.43)(p<0.001).

Economic analyses

Compared with routine care, active case finding was more cost-effective (£333 ($476) per additional case detected) than opportunistic case finding (£376) ($538) (table 5). The incremental cost-effectiveness ratio (ICER) for active case finding was £573($889) per additional case detected compared with opportunistic. Including patient-incurred costs made little difference to the results although alternative GP-led or Tariff models (where spirometry would be conducted in hospital outpatient appointments) were more expensive. ICERs for both opportunistic and active case-finding were lower when older age-groups or current smokers only were targeted, although at the expense of identifying many fewer cases. If no reminders were sent to patients, the opportunistic approach would be more cost-effective than the active approach. However, in every alternative scenario, active case finding identified more new cases than opportunistic case finding.

DISCUSSION

Identifying undiagnosed COPD remains an important priority worldwide. Despite little available evidence, national guidelines recommend opportunistic case-finding in the primary care setting.[15] However, in our large, generalisable, "real-life" RCT, very few new cases were identified in routine care. As expected, we demonstrated that a systematic targeted approach was markedly more effective than routine care at identifying new cases of COPD (adjusted OR 7.45 (95%CI 4.80, 11.55)). More importantly, we found that an active case-finding approach was twice as effective as opportunistic case-finding (adjusted OR 2.34 (2.06, 2.66)), and more cost–effective (£333 vs £376 per case detected).

In contrast to many previous studies, we sought clinical cases of COPD confirmed with spirometry. There is only one other relevant trial, undertaken among family medical practices in the US, which compares the effectiveness of a case-finding approach against usual care, although it did not confirm COPD with spirometry and may not be comparable to the UK or similar primary care settings.[11] Consistent with our findings, this trial demonstrated that a structured approach to case-finding using a screening questionnaire administered opportunistically was more effective than routine care in identifying new cases of COPD, although the effect size was smaller (OR=2.38) and diagnostic yield in routine care was lower than in our study (0.49% vs 0.8%).[11] In the literature there have also been many uncontrolled evaluations of case finding approaches for COPD with similar yields to our case-finding arm.[10] However, other than our pilot study,[21] our trial is the first to evaluate the most cost-effective method of administering an initial screening questionnaire, and to compare the results with routine care. The findings from this trial also confirm the results from our published model,[4] which suggested the likely superiority of active over opportunistic case finding.

In the active arm, around a third of eligible participants responded to the postal screening questionnaires, which was consistent with a trial in the Netherlands which compared two methods of processing a postal screening questionnaire,[22] and with uncontrolled studies described in our systematic review[10]. The response rate in our opportunistic arm was lower than we expected from our model[4] but similar to our pilot study[21] (13% on average across the practices and a maximum of 31%). Unlike other studies[10], our uptake rates include the whole eligible population as the denominator. It is also likely that our study reflects real life in busy UK primary care, where opportunistic administration of a questionnaire might not always be possible. Opportunistic response rates would need to be at least 40% (figure 1) to reach the yield observed with the active approach.

Our work builds on other published evaluations. A particularly relevant programme of work in the Netherlands – Detection, Intervention and Monitoring of COPD and Asthma (DIMCA) programme,

which began in 1991sought to detect subjects with signs of COPD and asthma at an early stage using a two-stage process of screening and monitoring, finding that 52% of adults aged 25-70 had early signs and symptoms of COPD or asthma, and 7.7% overall showed persistently decreased lung function or increased bronchial hyper-responsiveness.[23,24]

Our finding that newly identified cases tended to have mild or moderate airflow obstruction was in keeping with previous case-finding studies[10] and newly case-found patients were generally less severe than patients newly diagnosed in primary care.[25] Nevertheless, in accordance with our model, the majority of new cases could potentially benefit from inhalers,[26,27] self-management support,[28] smoking cessation[29] and vaccinations.[30] A substantial proportion (27%) also had significant breathlessness with potential to benefit from pulmonary rehabilitation.[31] However, it is important to note that the published evidence available on the effectiveness of these interventions may not directly apply to milder or case-found COPD patients for whom new studies are urgently needed.[32]

A notable strength of our trial was the achievement of high quality post-bronchodilator spirometry for COPD diagnosis. We have demonstrated the feasibility of undertaking excellent quality spirometry outside of a specialist setting with previously untrained staff, implementing a rigorous training programme and quality control system.

However, there were a number of practical difficulties. Using electronic searches of primary care records to identify ever smokers without prior COPD diagnoses was not always accurate. We acknowledge that there were more never smokers reported in the routine arm, which, as shown in sensitivity analyses (OR removing never smokers= 6.33 (4.12, 9.74)), may have slightly exaggerated the effect size. Although we aimed to exclude patients with a prior diagnosis of COPD using information from EHR records, 4.6% of the respondents to the screening questionnaire self-reported ever having been told that they had COPD, chronic bronchitis or asthma. However, this is unlikely to have influenced the direction of the results as only 10% of those newly diagnosed in our targeted arm reported having these conditions. Also, because of the large volume of participants, we were only able to invite patients for spirometry once, relying on reminder text messages (where possible) for those who did not attend to contact the office for further appointments. This led to lower attendance rates than expected, but was unlikely to make a substantial difference to the comparative effect size. Furthermore, we found it difficult to know with certainty what proportion of opportunistic questionnaires was administered, but it was clearly sub-optimal. Nevertheless, this was a pragmatic trial and these issues reflect real life in primary care. A further point of debate is the criteria of airflow obstruction we were required to use in our assessments in order to be comparable with current UK guidance. Use of the fixed ratio tends to overestimate the prevalence of new cases of COPD compared with the lower limit of normal alternative criteria[33] , particularly amongst older males. Use

of these criteria in the targeted arm attenuated the yield by about 25%; however it is unlikely that there would be any relative difference between the two arms if these criteria were applied to both.

For the future, it would be useful to identify more efficient ways to uncover new cases. In our study, in order to identify one new case of COPD, screening questionnaires had to be provided to 21 extra patients. Algorithms derived from GP records might better predict new cases of COPD and allow more efficient targeting of invitations, but require further testing.[34] Our sensitivity analyses also suggested that limiting to one postal reminder and targeting those aged 50+ might be less expensive with minimal loss in effectiveness. A postal-only approach would be nearly as effective and avoid the need for opportunistic administration during busy consultation times.

Finally, before a national case finding programme could be recommended, the longer term effects of case-finding on health outcomes should be studied. The DIMCA programme in the Netherlands suggested that long-term prognosis might not be improved by screening.[24] It would be important to establish whether earlier identification using our approach would lead to effective management and health gains which would outweigh the cost to the health service of the medications and management and the potential cost to the patient of having a "label" of COPD. Currently, there is insufficient evidence of this.

In conclusion, in this well-established primary care system, routine practice identified few new cases. An active targeted approach is a highly effective and also cost-effective way to identify patients with undiagnosed clinically important COPD and has the potential to improve their health.

CONTRIBUTORS

The concept of a need for the trial was identified by RJ/PA and the design was refined and shaped in discussion with DF and KKC. AS undertook the statistical analyses with guidance and input from RR and JM. JM undertook the randomisation. DB and SJ undertook the economic analyses. AE, MM, BC, SH designed the approach to training and spirometry quality control procedures. RJ wrote the first draft and led the oversight of the trial with PA, DF and AE. All authors inputted to the design, analysis and manuscript.

DECLARATION OF INTERESTS

KKC reports grants from Pfizer China, outside the submitted work.

RS reports personal fees from Boehringer Ingelheim, personal fees from GSK, personal fees from Chiesi, personal fees from Takeda, personal fees from Novartis, personal fees from Polyphor, grants from CSL Behring, grants from Talecris, personal fees from Dyax, outside the submitted work.

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All other authors have nothing to disclose.

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Table 1 Screening process assumptions and costs

Process	Assumption	Source	Cost per patient (£)
Searches of patient records, screening and flagging notes with prompts			
Running the search	20 minute of practice manager time per practice	Estimate from trial	0.01
Screening patient list	1 minute of GP time per patient selected	NIHR costing report	3.20
Attaching prompts	15 seconds of administration time per patient record	Estimate from trial	0.94
		Total	**4.14**
Invitation letters and questionnaires			
Drafting/approving letter	1 hour of practice manager time per practice per mailout	NIHR costing report	0.05
Administering mail-merge x 3	2 hours of administration time per practice per mailout	NIHR costing report	0.08
Administering the postal questionnaires	1.8 minutes of administration time per letter sent, plus stationery cost	NIHR costing report	0.67
Stationery cost for postal questionnaire	6 sheets of headed note paper & letter head, stamp, envelope & prepaid return envelope	NIHR costing report	1.74
		Total per questionnaire/reminder	**2.55**
Completing the questionnaire in-clinic	6 sheets of headed notepaper & 1 minute of GP time per questionnaire completed in clinic	NIHR costing report, estimate from trial	**3.84**
Processing questionnaires and allocating appointment times	30 minutes of administration time per questionnaire completed	Estimate from trial, NIHR costing report	**11.23**
Appointment booking			
Book appointments	10 minutes plus stamp, letter and envelope for 100% of appointments and text message for 49% of appointments	Estimate from trial , NIHR costing report	4.32
Proportion of patients that cancelled or rebooked	All booked appointments divided by appointment attended		1.91
		Total per appointment	**8.26**
Spirometry			
Staff costs	50 minutes clinical support worker time, 3 minutes of reception time	Estimate from trial	22.04
Training	4 weeks training, plus 2-day workshop, 1-day refresher course. Annual cost, assuming 372 tests per year and 3-yearly reassessment	Estimate from trial	4.33
Room costs	50 minutes per appointment (allowing for DNAs)	Estimate from trial	12.55
Travel costs	Average 2.85 miles per attendance, 40p per mile	Estimate from trial	1.14
Equipment	Use of spirometer and laptop. Single use of mouthpiece, spacer and salbutamol.	Estimate from trial	10.87
		Total	**50.95**

DNA = Did not attend. NIHR costing report: http://www.crn.nihr.ac.uk/resources/resource-template/ (Accessed 11th August 2015)

Table 2 Baseline characteristics of randomised general practices

	Targeted case finding	Routine care
Practice characteristics		
Total practices	27	27
Practice list size	5762 (3482)	5811 (3451)
IMD score	35.2(25.0,51.9)	36.0 (19.7,46.3)
% white patients	80.5 (20.5)	79.1 (21.9)
% age 45+ years	38.5 (34.2,43.4)	38.2 (33.1,43.4)
Diagnosed prevalence of COPD (%)	1.6 (0.6)	1.7 (0.7)
Patient characteristics		
Total patients	32,789†	42,029
Sex (male)	17,864 (54.5)	21,659 (51.5)
Age (Years)	55.3 (47.5, 65.5)	55.6 (47.6, 66.1)
Ethnicity		
White	18,186 (55.5)	23,925 (56.9)
Mixed	265 (0.8)	223 (0.5)
Asian	1,742 (5.3)	2,044 (4.9)
African Caribbean	1,220 (3.7)	1,025 (2.4)
Other	591 (1.8)	353 (0.8)
Missing	10,785 (32.9)	14,459 (34.4)
Smoking status		
Never smoker	6,580 (20.1)	10,949 (26.1)
Ex-smoker	13,857 (42.3)	16,685 (39.7)
Current smoker	11,924 (36.4)	14,222 (33.8)
Missing	428 (1.3)	173 (0.4)
Comorbidities**		
Asthma	3117 (11.1%)	3834 (9.3%)
Ischaemic heart disease	1881 (6.7%)	2341 (5.7%)
Chest infection in previous 3 years	2694 (9.6%)	4377 (10.6%)
Number of patients sharing household		
1	22,421 (68.4)	24,261 (57.7)
2*	9,646 (29.4)	16,104 (38.3)
3 or more*	722 (2.2)	1664 (4.0)

Figures in this table are mean(SD), median(Q1,Q3) or n(%) as appropriate.

*patients reside in the same household

** From 22 targeted practices (28,025 patients) and 26 routine practices (41,100) with available data

IMD=Index of multiple deprivation

†results exclude 22 randomised patients who withdrew their data

Table 3 Effectiveness of active compared with opportunistic case finding‡

	Active **N (%)**	**Opportunistic** **N (%)**	**Total** **N (%)**
Total patients approved by GP for contact	15378	15387	30,765
Deceased by 12 months	93 (0.6)	92 (0.6)	185 (0.6)
Left practice by 12 months	870 (5.7)	897 (5.8)	1,767 (5.7)
Primary Outcome (NICE criteria)[15]			
COPD trial-identified (post BD FEV1/FVC 0.7)	662 (4.3)	189 (1.2)	851 (2.8)
Additionally identified by GP	160 (1.0)	181 (1.2)	341 (1.1)
Total COPD diagnosed	**822 (5.4)**	**370 (2.4)**	**1,192 (3.9)**
Crude Risk difference (95% CI)	0.029 (0.025, 0.034)		
Crude Relative risk (95% CI)	2.22 (1.97, 2.51)		
Adjusted OR (95%CI)*	**2.34 (2.06, 2.66) (p<0.001)**		
Adjusted risk difference (95%CI)* †	**0.029 (0.023, 0.036) (p<0.001)**		
Characteristics of patients newly diagnosed through trial			
Total number	662	189	851
Severity of airflow obstruction			
Mild ($FEV_1 \geq 80\%$ predicted)	352 (53.2)	107 (56.6)	459 (53.9)
Moderate ($FEV_1 < 80\%$ and $\geq 50\%$ predicted)	288 (43.5)	72 (38.1)	360 (42.3)
Severe ($FEV_1 < 50\%$ and $\geq 30\%$ predicted)	19 (2.9)	10 (5.3)	29 (3.4)
Very severe (FEV1<30% predicted)	3 (0.5)	0 (0.0)	3 (0.4)
Breathlessness (MRC dyspnoea score Grade 3 or more)	172 (26.0)	59 (31.2)	231 (27.1)
Current smoker	244 (36.9)	59 (29.6)	300 (35.3)
Prior self-report of COPD/chronic bronchitis/emphysema	74 (11.2)	18 (9.5)	92 (10.8)

*adjusted for GP practices, IMD score of practice, patient age, patient ethnicity using logistic regression

†obtained using estimate of RR of 2.30 (2.01, 2.58) from multilevel Poisson regression model with random effects and robust standard errors, together with the 2.4% baseline risk estimate from routine group

BD=bronchodilator ‡results exclude 22 randomised patients who withdrew their data

Table 4 Effectiveness of targeted case finding compared with routine care‡

	Targeted case finding **N (%)**	**Routine care** **N (%)**
Total eligible patients	32789	42029
Deceased	255 (0.8)	527 (1.3)
Left practice	1,972 (6.0)	2,492 (5.9)
Primary Outcome (NICE criteria)[15]		
COPD trial-identified (post BD FEV1/FVC <0.7)	851 (2.6)	-
Additional patients identified by GP	427 (1.3)	337 (0.8)
Total COPD newly diagnosed	**1,278 (3.9)**	**337 (0.8)**
Crude risk difference (95% CI)	0.031 (0.029, 0.033)	
Crude relative risk (95% CI)	4.86 (4.32, 5.48)	
Adjusted OR (95%CI)*	**7.45 (4.80, 11.55)(p<0.001)**	
Adjusted risk difference (95%CI)*†	**0.049 (0.030, 0.077)**	

*adjusted for clustering of GP practices, IMD score of practice, patient age, patient ethnicity using multilevel logistic regression

†obtained using adjusted estimate of RR (7.23 (4.10, 10.37)) from multilevel Poisson regression model with random effects and robust standard errors, together with the baseline risk estimate of 0.8% from routine group

BD= bronchodilator

‡results exclude 22 randomised patients who withdrew their data

Table 5 Results of the cost-effectiveness analysis with sensitivity analyses

	Active vs routine care				**Opportunistic vs routine care**			
Scenario	New cases identified in the active arm*	Difference in mean per patient costs (£)	Adjusted difference in mean cases detected	Cost per additional case detected (£)	New cases identified in the opportunistic arm*	Difference in mean per patient costs (£)	Adjusted difference in mean cases detected	Cost per additional case detected (£)
Base case	822 (100%)	23.15	0.0696	333	370 (100%)	7.95	0.0211	376
Including patient costs		23.64	0.0696	340		8.04	0.0211	381
GP led model†		28.97	0.0696	416		9.47	0.0211	448
Community model†		23.53	0.0696	338		8.05	0.0211	381
Tariff model†		26.28	0.0696	378		8.77	0.0211	415
Altering target groups:								
Ever smokers only	707 (86.0%)	23.10	0.0753	307	322 (87.0%)	7.69	0.0219	351
Current smokers only	317 (38.6%)	21.30	0.0744	286	164 (44.3%)	7.29	0.0242	301
Aged 65+	378 (46.0%)	26.31	0.1282	205	204 (55.1%)	9.53	0.0477	200
Aged 60+	534 (65.0%)	26.23	0.1089	241	264 (71.4%)	9.26	0.0380	244
Aged 55+	646 (78.6%)	25.69	0.1029	250	302 (81.6%)	9.00	0.0320	281
Aged 50+	733 (89.2%)	24.90	0.0941	265	336 (90.8%)	8.47	0.0291	291
Aged 45+	786 (95.6%)	23.99	0.0813	295	355 (95.9%)	8.26	0.0248	333
Altering triggers for spirometry invite:**								
Cough & phlegm only	383 (46.6%)	17.36	0.0236	735	234 (63.2%)	6.25	0.0086	725
Dyspnoea only	655 (79.7%)	20.66	0.0524	394	316 (85.4%)	7.33	0.0164	446
Excluding wheeze	713 (86.7%)	21.46	0.0580	370	336 (90.8%)	7.49	0.0181	414
Altering processes**								
3 month period for recruitment	786 (95.6%)	22.35	0.0658	340	311 (84.1%)	6.94	0.0143	484
1 reminder	740 (90.0%)	21.59	0.0610	354	370 (100%)	7.95	0.0211	376
0 reminders	589 (71.7%)	19.01	0.0441	431	370 (100%)	7.95	0.0211	376

*raw numbers only, given as n (% of base cases identified)

** alternative scenarios assume that additional patients are not diagnosed outside of the trial processes instead † details provided in appendix 4

Figure 1 Schema of TargetCOPD case finding RCT †

†Note that search terms were applied to electronic health records in order to identify ever smokers, but any patients found to be never smokers were included in the primary analysis in order to maintain the pragmatic approach.

After the randomisation level, values exclude 22 patients who withdrew their data.

*% of all approved patients randomised to nested trial **% of all eligible in cluster comparison