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Synopsis

Sputum colour charts to guide antibiotic self-treatment of acute exacerbation of chronic obstructive pulmonary disease: the Colour-COPD RCT

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Disclaimer: This article contains transcripts of interviews conducted in the course of the research and contains language that may offend some readers.

Abstract

Background: Chronic obstructive pulmonary disease exacerbations (acute exacerbation of chronic obstructive pulmonary disease) are characterised by increased sputum volume, purulence and breathlessness. Patients are encouraged to recognise and treat acute exacerbation of chronic obstructive pulmonary disease as part of a self-management plan. Only half of acute exacerbation of chronic obstructive pulmonary disease are caused by bacterial infection, but self-management plans generally advocate use of antibiotics and steroids for all events, hence antibiotics may be overused. Sputum colour relates closely to bacterial load; thus it could determine whether antibiotics are appropriate. This pragmatic randomised controlled trial tested whether use of a sputum colour chart is safe and effective in United Kingdom primary care.

Methods: Colour chronic obstructive pulmonary disease was a multicentre, randomised controlled trial in adults with chronic obstructive pulmonary disease who had ≥ 2 acute exacerbations of chronic obstructive pulmonary disease or ≥ 1 hospital admission for acute exacerbation of chronic obstructive pulmonary disease in the preceding year. The primary objective was to demonstrate that the Bronkotest® (London) sputum colour chart is non-inferior to usual care (safe). The primary outcome was rate of hospital admission for acute exacerbation of chronic obstructive pulmonary disease at 12 months; secondary outcomes included requirement for second courses of treatment and quality of life (chronic obstructive pulmonary disease assessment test score). Nested substudies examining daily symptoms via an e-diary and sputum culture assessed untreated acute exacerbation of chronic obstructive pulmonary disease rate and antibiotic resistance, respectively. A process evaluation examined trial fidelity and acceptability of the intervention, employing qualitative research methods incorporating patients as co-researchers.

Limitations: The study was terminated early due to low recruitment (115/2954 planned sample size).

Results: One hundred and fifteen patients were recruited and randomised 1 : 1 to colour chart use or usual care; they generally had severe Global Initiative for Chronic Obstructive Lung Disease D chronic obstructive pulmonary disease, with significant breathlessness (54% Medical Research Council score of 4 or 5) and poor quality of life

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(chronic obstructive pulmonary disease assessment test score at baseline 24). Comorbid respiratory and systemic disease was common. Self-management was delivered well in both arms, and the colour chart acceptable to patients and staff; no specific issues for patients with multiple long-term conditions were identified. Hospital admissions for acute exacerbation of chronic obstructive pulmonary disease tended to occur more in colour chart users [32 vs. 16%, relative risk 1.95 (0.92 to 4.18)], and antibiotic courses within 14 days of initial acute exacerbation of chronic obstructive pulmonary disease treatment were also more common [34 vs. 18%, adjusted relative risk 1.80 (0.85 to 3.79)]. Despite this, quality of life was better in colour chart users at 12 months [chronic obstructive pulmonary disease assessment test 19.9 vs. −24.5, adjusted mean difference −2.95 (−5.93 to −0.04)]. Thirty-eight patients consented to the sputum substudy, and 57 samples were received (42 stable state, 15 during acute exacerbation of chronic obstructive pulmonary disease), of which 30% contained a potentially pathogenic bacterium. Sputum was more likely to be purulent in subjects with bronchiectasis, independent of disease state (stable vs. exacerbation) or whether the sample was positive for a potentially pathogenic bacterium, suggesting that colour alone cannot be used to guide antibiotic use. Eleven patients completed the e-diary study, and 42 symptom-defined acute exacerbation of chronic obstructive pulmonary disease events were captured, many of which were untreated, exhibiting lower EXAcerbations of Chronic Pulmonary Disease Tool scores than those which were treated. Untreated events were slower to settle. Differences between study arms were not meaningful to compute due to low numbers.

Conclusion and future work: Our results imply that the Bronkotest sputum colour chart is unlikely to be a useful addition to self-management for chronic obstructive pulmonary disease patients in primary care, but further work is required to confirm this.

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Introduction

This synopsis describes the methods and limited results from a pragmatic open-label study, where patients were to be randomised from primary care, which terminated early due to low recruitment. On 14 November 2022, we met with the NIHR to discuss the feasibility of Colour-COPD continuing to hold funding to reach its recruitment target. On 30 November 2022, we were informed that the NIHR would cease funding Colour-COPD. The trial closed to recruitment on 30 March 2023 (after amendments to reduce trial processes were approved), and it was agreed that participants would be followed for 12 months when the primary outcome was collected. As the trial has terminated early, with much lower numbers of patients than expected, due to the slow recruitment post pandemic, limited conclusions can be drawn. The trial team felt it was not worthwhile pursuing separate papers for the trial protocol independent of the synopsis, but there is a threaded publication for our qualitative work package. In this report, we also detail some lessons learnt for future trialists who wish to study care pathways for chronic obstructive pulmonary disease (COPD), in particular in primary care.

Background

What is the problem?

Chronic obstructive pulmonary disease is a chronic condition affecting 2 million people in the UK, causing over 140,000 hospital admissions and 1.7% of UK hospital bed-days per year.[1] Common day-to-day symptoms include breathlessness, which is typically worse on exertion, and cough productive of sputum. Chronic obstructive pulmonary disease is defined by airflow obstruction on spirometry, this being a ratio < 0.7 and lower than the lower limit of normal for age in the forced expiratory volume in 1 second (FEV1) and forced vital capacity after administration of a bronchodilator. Chronic obstructive pulmonary disease severity was historically determined by the degree of FEV1 impairment relative to a normal individual of the same age, sex and height, expressed as the percentage predicted for age. A variety of studies have derived these normal values, most recently using the Global Lung Function Initiative (GLI) equations,[2] designed to be race-neutral after significant debate about the value of using race-specific equations.[3] It is also possible to define severity as described by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) outcomes strategy.[4] At commencement of this trial, this used four categories, illustrated in *Figure 1*. In this system, category C and D patients have ≥ 2 exacerbations/year or ≥ 1, which results in hospital admission and are distinguished by their degree of breathlessness [Medical Research Council (MRC) score] or quality of life [COPD assessment test (CAT) score]. Patients in category D have a high symptom burden, as well as exacerbations, whereas category C patients have fewer day-to-day symptoms. More recently, GOLD merged categories C and D into one, termed 'E' in recognition of the fact that prior exacerbation rate appears to be the most significant factor in determining treatment and describing prognosis.

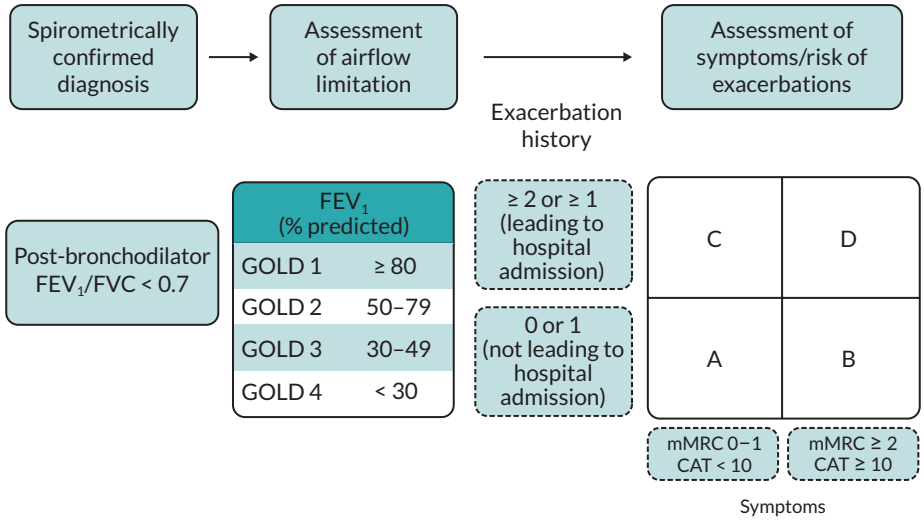

FIGURE 1 Severity of COPD according to GOLD outcomes strategy. FVC, forced vital capacity.

Most admissions to hospital in COPD patients are for exacerbations of COPD [acute exacerbation of chronic obstructive pulmonary disease (AECOPD)]. Exacerbations are defined by 'worsening of respiratory symptoms beyond normal day-to-day variations and leading to a change in medication'.[4] Cardinal symptoms include altered sputum volume and/or colour and worsening dyspnoea.[5] Exacerbation pathophysiology is not fully understood but includes elements of infection and of environmental triggers.[6,7] A systematic review in 2012 found bacteria in just 46% of events,[8] suggesting antibiotics will effectively manage only half of AECOPD episodes; nevertheless, they are used in the majority of events. Subtypes of exacerbation can be classified according to symptoms (type 1 = increased volume and purulence of sputum and worsening breathlessness, type 2 = 2 out of 3 of these symptoms and type 3 = worsening breathlessness with no other symptom[5]) or healthcare use (mild = increased inhaler use alone, moderate = primary care visit, antibiotic or steroid use, severe = hospitalisation, or unreported[9]). Data from trials and cohort studies suggest that 50–70% of exacerbations identified through daily diary reporting are unreported, and there is evidence that patients with unreported exacerbations have poorer prognosis with faster lung function and health status decline compared with those who have no unreported events.[10–12] Increasing AECOPD frequency generally leads to faster disease progression,[13] and hospitalisation for AECOPD predicts mortality.[14,15] The evidence on whether prognosis differs according to the underlying cause of AECOPD (bacterial, viral or non-infective) is inconsistent.[16] Therefore, it is important for trials where AECOPD are an outcome to capture overall AECOPD rate, including hospitalised and unreported events.

One approach to reduce the impact of exacerbations is the use of self-management (SM) plans, alongside a pack of antibiotics and steroids [rescue pack RP)].[17] Evidence for SM as a means of reducing admission in COPD is inconsistent[18] and heterogeneous.[19] Multidisciplinary SM support programmes, including action plans for AECOPD management, are effective in reducing admissions when they include iterative feedback to patients.[20] A systematic review conducted by our group attempted to delineate the effect of each component of SM, of which simple action plans for AECOPD management are one; we did not find an effect of any one component on outcomes, including hospital admissions and AECOPD rates.[19] In the UK, many patients are given an action plan alongside a pack of steroids and antibiotics, which they are advised to use for AECOPD, but often with little education on when and how to use these. Iterative feedback is not usually provided, and instead, most use a traffic light system to determine whether medical help should be sought or treatment taken. Furthermore, UK health professionals have identified numerous training needs to deliver iterative SM.[21] Based on the evidence from trials, SM plans as currently used in usual care in the UK (i.e. simple action plans with little ongoing support), are unlikely to reduce hospitalisations. This evidence that SM plans as used in usual NHS care do not alter hospital admission rates was the primary reason for choosing a non-inferiority design in this trial, rather than hypothesising that a colour chart within a SM plan could influence admissions by either increasing or decreasing them. Furthermore, if the sputum colour chart safely reduced antibiotic usage without an increase in treatment failure, including hospital admissions, then this would be the preferred strategy.

Chronic obstructive pulmonary disease is associated with an increased incidence of cardiovascular, psychiatric and musculoskeletal morbidity. Comorbidity in COPD influences mortality[22] and health-related quality of life (HRQoL)[23] as well as sharing aspects of pathogenesis.[24]

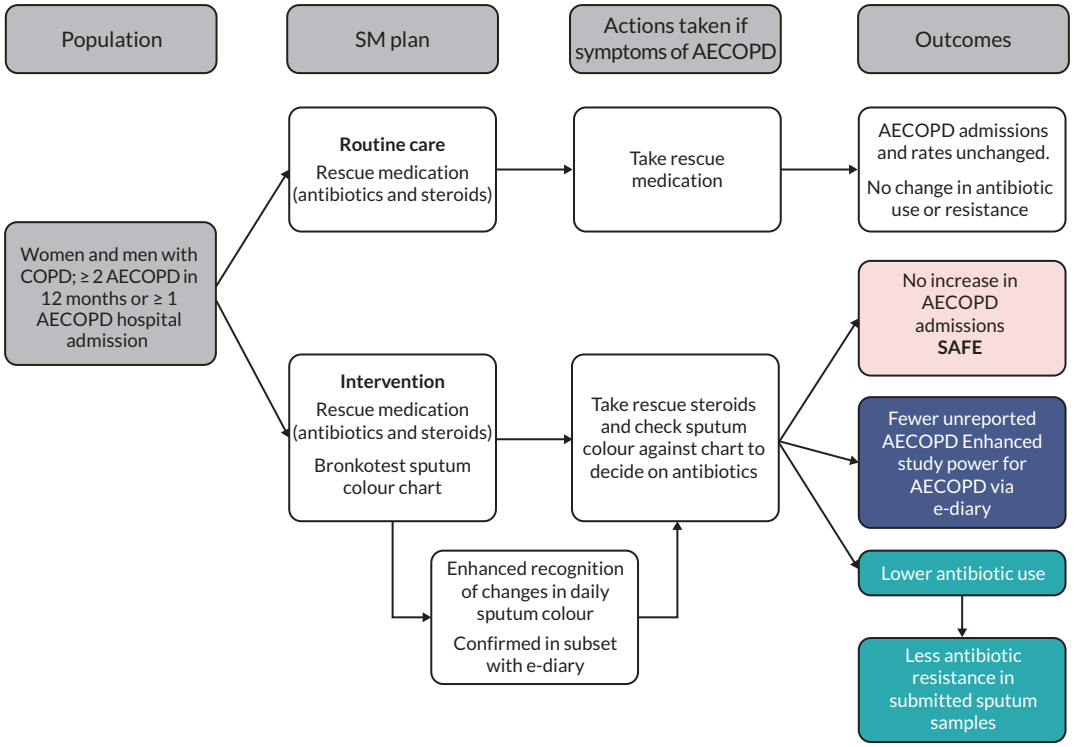

FIGURE 2 Logic model for Colour-COPD study.

Assessing comorbidities actively in usual COPD has been recommended by a number of guidelines,[25] as management of these may improve outcome.[26] Some comorbidities adversely affect survival,[22,27] hence supporting a process of active assessment and treatment of these conditions. It is also conceivable that comorbidities which have similar symptoms to COPD may impact upon ability to self-manage, such that collecting data on multimorbidity would be important in any trial of SM.

Why this research was conducted

This study addressed the problem of personalising and optimising effectiveness of AECOPD management. Each year, around half of all patients with COPD have frequent AECOPD (≥ 2 per year[28]), and in the UK, 44–85% of patients with this AECOPD rate were hospitalised again within 12 months.[29] AECOPD admissions drive the economic burden of COPD, which is significant both in the UK and worldwide.[30] Rapid re-admissions are also common – the national COPD audit has shown that 43% of patients with COPD who were admitted are back in hospital within 90 days,[15] and up to 71% by 12 months.[31] Intuitively, early recognition and treatment of AECOPD would reduce exacerbation severity and duration, and improve prognosis; evidence for this is limited but supportive.[10] However, only half[8] of all exacerbations are bacterial and would require treatment with antibiotics, suggesting that overuse of antibiotics occurs when RPs containing both antibiotics and steroids are given. Inappropriate use or overuse increases the long-term risk of antibiotic resistance,[32] and reducing antibiotic resistance through appropriate stewardship is a recognised NHS priority. In hospitalised AECOPD patients, resistance occurs in up to 66% of cases, and relates to past antibiotic use,[33] suggesting those with prior hospitalisation or frequent antibiotic courses are a key group to target for interventions aimed at reducing resistance.

Sputum colour is a marker of neutrophilic inflammation and bacterial infection,[34] suggesting it could be used to guide antibiotic treatment and reduce inappropriate use. In studies conducted in Birmingham in approximately 100 patients over a year,[34] there was 94% probability that infectious exacerbations of COPD had green sputum (sensitivity of green sputum = 94%). Specificity of green sputum for bacterial infection was 77%. This suggested that sputum colour was a tool with potential to reduce inappropriate antibiotic use, and a definitive study to test this was required. The logic model for the study is shown in *Figure 2*.

Aims and objectives

Primary objective

Our primary objective was to assess whether use of the 5-point sputum colour chart, alongside a SM plan and RP containing 5 days of antibiotic and steroid treatment (the

intervention) is safe, as defined by being not substantially worse compared to use of the plan and pack alone (best usual care) for patient hospitalisation admission for AECOPD at 12 months post enrolment (defined by randomisation time point).

Secondary objectives

Our secondary objectives were to:

1. Assess whether the intervention is safe, as defined by the rate of 30- and 90-day AECOPD re-admissions, rate of treatment failure (defined by ongoing symptoms and/or requirement for treatment in the 14 days after a self-managed event), and time to next AECOPD after a self-managed event.
2. Determine whether use of the intervention is effective at 12 months after enrolment in terms of reducing self-reported antibiotic use when compared to best usual care, including RP, as well as reducing adverse events related to antibiotics (e.g. oral thrush).
3. Describe the effect of the intervention on number of unscheduled general practitioner (GP) attendances, for AECOPD, in the 12 months post enrolment.
4. Describe the effect of the intervention on unreported AECOPD rate through a substudy using daily symptom diaries. Unreported AECOPD are defined by daily symptom change in the absence of input from a healthcare professional (HCP), or reporting symptom change to a HCP.
5. Describe the effect of the intervention on antibiotic resistance patterns in sputum of people with COPD. This substudy also allows us to assess the appropriateness of antibiotic use by objectively confirming sputum colour at AECOPD and confirming presence of bacteria.
6. Assess fidelity of delivery of the intervention by use of a checklist inquiring on critical features of education around colour chart and SM plan use.
7. Assess adherence to SM plan advice by comparing use of AECOPD treatment to daily symptoms (e-diary subgroup only).
8. Explore social acceptability and practical responses to the intervention by interviewing both staff delivering the intervention and participants receiving the intervention.
9. Determine the cost-effectiveness and cost-utility of using a colour chart as part of a SM plan.

Exploratory objective

During the study, we were successful in getting add-on funding to explore the impact of multimorbidity; this had the objective of examining whether multimorbid patients responded differently to the intervention.

We were unable to address our main objective, nor most of our research questions, due to early termination of the study at < 10% of planned participants. The e-diary substudy should have allowed us to determine if unreported AECOPD are impacted upon by the intervention, and their rate in UK primary care; as well as assessing adherence to the intervention's advice accurately, but there were so few patients in this element that conclusions are limited. Health economic analysis was not commenced.

Methods

Research design: lessons learnt

Colour-COPD was designed as a randomised controlled trial (RCT) of a simple change to COPD SM, namely adding a colour chart to the SM plan issued as part of best practice usual care. We chose a non-inferiority design because evidence from trials showed that SM plans as currently used in usual care in the UK (i.e. simple action plans with little ongoing support) are unlikely to reduce hospitalisations. A superiority design would hypothesise that a colour chart within a SM plan could influence admissions either by increasing or decreasing them. This design, using conventional statistics for power calculations, had resulted in a sample size that appeared feasible across 80 GP practices over 2 years, based on national prevalence data. In order to maximise feasibility, we kept our data collection simple – most data could be collected from the routine primary care record in the annual review for COPD; we reviewed current templates for these in System One and EMIS (commonly used electronic medical records in primary care) to ensure that our case report forms (CRFs) at baseline and 12-month follow-up adhered fairly closely to these. However, we did not use a design that collected data purely from the medical record because of concerns about missing data that may be pertinent to describing confounders, such as COPD severity. Extraction of spirometry from the primary care record can be challenging, because data are not always entered to templates and may be scanned in as separate documents. We also chose to collect data on chronic bronchitis, as a known risk factor for AECOPD,[35] and a criterion for enrolment in the sputum substudy, which is rarely recorded in the primary care record. Educational level was also collected, in case this related to understanding of SM principles (as has since been shown in cardiovascular disease[36]); this would not typically be recorded in routine primary care. Extraction of outcome data for AECOPD events can also be difficult because

there is no single code for an AECOPD event, and packs of treatment will be issued without the occurrence of an event, so that the patient can self-manage. Since inception of this trial many groups have become more familiar with use of the routine record for trial outcomes, and advances are being made in using primary care respiratory data, such that if designing the study now we might consider such a design, which would have been even easier for sites. It is also likely in a trial of this planned size (around 3000 patients) that most confounders would have balanced across arms because of the randomisation process, and while we could not have described all confounders, it might still have been feasible to rely on the healthcare record. However, feasibility of data collection was not the primary reason for this trial ceasing before reaching its conclusion – we were unfortunate in being ready to start in March 2020, at which time health services, especially in primary care, changed markedly due to the pandemic.

We recognised that delivery of personalised SM might not occur in the ideal manner during time-pressured COPD reviews, and that if SM was delivered badly, it may have no effect. Hence, we arranged for data collection pertaining to fidelity of intervention delivery to be collected. To further reduce burden on primary care staff, this was done by telephone by the trials unit (as well as patient self-report), such that primary care staff only needed to see patients for the study at baseline and follow-up, as they would for routine COPD care. This worked reasonably well from a technical perspective, but the conclusions emerging about fidelity of delivery differed between the categorical data obtained during calls compared to the later qualitative study. There are a variety of ways in which to assess fidelity,[37] and we chose a comprehensive approach of direct observation (by video-recording), checklists and in-depth interviewing. We found there appears to have been disparity in patient recall regarding their understanding of SM plan delivery between the fidelity phone calls and the interviews for the qualitative substudy, thus in future we would choose one method only to avoid confusion of results. It is possible the video-recording would have been even more informative, and not subject to recall biases, but it was not possible to deliver this by a separate recording team with social distancing requirements. We considered a camera that staff could wear themselves, which would have been less intrusive anyway, but budgetary cuts meant this could not occur either.

When the pandemic occurred, we made some adaptations to study design to improve deliverability – we enabled remote consultation for SM plan education, and planned to collect data on how the consultation was conducted – face to face, over video or over the telephone – to assess whether the mode of delivery impacted on efficacy or fidelity. None of the adaptations made a significant impact on recruitment rate such that early termination had to occur.

Study population and rationale

Setting

Since most SM advice is generally issued in primary care, the study setting was chosen to be primary care. However, recruitment issues during the pandemic eventually caused us to expand our sites into secondary care as well.

Included patients had:

- Clinically diagnosed COPD, confirmed by a medical record of postbronchodilator spirometry denoting obstruction.
- ≥ 2 AECOPD in the 12 months prior to screening according to the patient or ≥ 1 hospital admission for AECOPD.
- Been able to safely use SM plan in the view of their usual-care practitioner.
- Been able to use sputum colour chart; this will be confirmed by a sight test if there is any doubt on initial assessment by the usual care or research team. Patients who report being colour blind will have their ability to use the chart tested at the screening visit.
- Age ≥ 18, with no upper limit.
- Written informed consent given.
- Additionally, to participate in the e-diary substudy:
  - Access to smartphone/tablet and an e-mail address.

- Additionally, to participate in the Sputum substudy:
  - Chronic bronchitis, defined by self-reported sputum production for at least 3 months in each of 2 consecutive years or more.

Exclusion criterion was:

- Household member already participating in the study.

The rationale for including patients with spirometrically confirmed disease was to ensure the population in the trial definitely had COPD, since this is the test required to confirm its presence. Misdiagnosis is common in primary care,[38] often driven by misinterpretation of spirometry; hence we wanted to review the data from prior spirometry to ensure that fixed airflow obstruction was present. Frequently exacerbating or previously admitted patients were chosen because AECOPD rate is a key predictor of future rate,[28] such that this should ensure adequate event

rate and power in the study. We kept inclusion criteria broad and did not exclude overlapping respiratory conditions because dual coding constitutes a large proportion of the COPD population in primary care; 22% of COPD patients are also coded to have asthma[39] and 29% are found to have bronchiectasis on CT scan.[40] Including such patients kept our results generalisable.

We considered when budgeting for the study whether to select an e-diary which operated on the patients' own device or on one provided by the study. Ultimately, keeping costs down was the main factor which drove us to use the patients' device, and had the study recruited to target we would have compared the e-diary population to that of the main study for demographic factors potentially indicative of equity issues in that substudy, such as digital exclusion due to age or financial issues. An e-diary study was the only way to capture unreported AECOPD events.

The sputum substudy required submission of samples in the stable state, which can only reliably be done if sputum is produced regularly, hence the criterion of chronic bronchitis.

Intervention and control

The intervention was a Sputum colour chart use of the 5-point sputum colour chart, adapted from Bronkotest® used alongside a SM plan and RP containing 5 days of antibiotic and steroid treatment. Several sputum charts are available. We chose the 5-point sputum colour chart, adapted from Bronkotest and illustrated in *Figure 3* from among these because:

1. The 5-point sputum colour chart, adapted from Bronkotest, is the only one that has been validated for use in COPD.
2. It has been validated against sputum bacterial load – 84% of purulent samples (darker green colour) contained bacteria compared to 38% of mucoid (lighter colour) samples.[34]
3. The 5-point sputum colour chart, adapted from Bronkotest, is commercially available and inexpensive (< £2 per patient).
4. It was practical to use in UK primary care by patients to guide therapy;[34] patients using the chart to guide antibiotic use rarely experienced treatment failure.[41]
5. Bronkotest resources are available to train healthcare providers on its use; this will facilitate smooth study set-up and will be used at study commencement and site initiations. In short, patients will be advised only to use the antibiotic component of their pack if their sputum is green, or significantly changed from their baseline colour. All patients will be advised to use oral steroids from their pack if they have symptoms consistent with a non-infective AECOPD (sputum not green).

Other available colour charts have a lower degree of validation, or are less practical to use. For example, the colour chart developed by Allegra *et al.* was found to be too complex in clinical practice, and there was insufficient agreement between physicians' and patients' colour ratings.[42] Another chart designed primarily for nasal mucus, with the purpose of enhancing antibiotic stewardship, has no published validation studies supporting its use.[43]

The comparator was usual care, specifically including a standardised SM plan.

In primary care, this currently consists of a simple, written SM plan and RP of 5 days' antibiotic and steroid treatment, with the duration of treatment being based on evidence

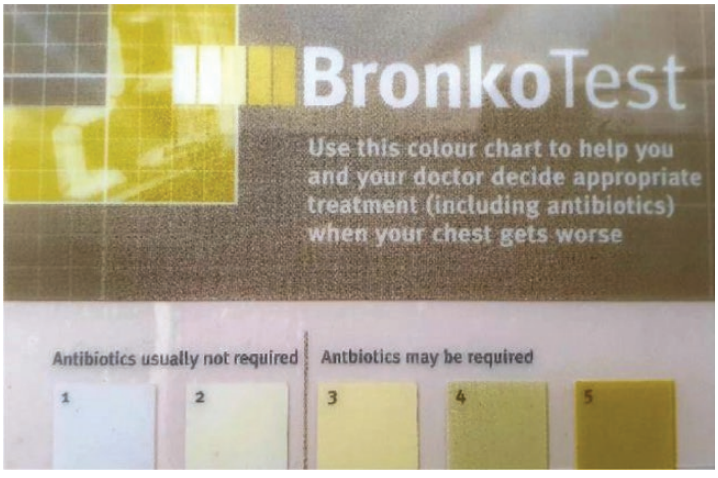

FIGURE 3 Bronkotest colour chart.

from systematic reviews.[44] However, we were mindful of variation in how it is implemented in practice. For example, analysis of our data from the Birmingham COPD cohort study, including around 1000 patients from primary care, showed that fewer than half (45%) had an agreed SM plan at recruitment in 2012. Since then, a local pay for performance incentive is likely to have increased rates, but variation remains likely. To standardise the SM component of treatment for patients in both arms, we adapted the current NHS Salford SM plan as a template. We chose this plan because the pages on AECOPD management were derived from a nationally (British Lung Foundation) endorsed resource, are simple to read and are already in use in one of the two major areas we plan to recruit from. Patients in the usual-care group were advised to treat any AECOPD with both RP elements, whereas intervention group patients used their chart to guide antibiotic use.

Outcomes

Primary outcome

A binary outcome assessing incidence of at least one AECOPD over 12 months post randomisation, where patients needed hospitalisation (defined by hospital discharge letter/coding). Incidence of AECOPD was obtained from patient reports and recorded on CRFs.

Secondary outcomes

1. Self-reported AECOPD (including those for which admission is required) obtained by telephone calls to patients every 3 months.
2. Self-reported antibiotic for AECOPD, and all-cause steroid prescriptions at 12 months post randomisation.
3. All-cause hospital admission, participant self-report at 12 months post randomisation.
4. Re-admissions to hospital for AECOPD at 30 and 90 days, participant self-report at 12 months post randomisation.
5. Bed-days due to AECOPD at 12 months post randomisation.
6. Mortality, as determined by the medical record, at 12 months post randomisation.
7. Self-reported GP visits, for AECOPD at 12 months post randomisation.
8. Self-reported prescriptions for second courses of antibiotics within 14 days of self-reported event (defined as treatment failure) at 12 months post randomisation.
9. Self-reported prescriptions for antifungals (e.g. for oral thrush) at 12 months post randomisation.
10. Quality of life [COPD assessment test (CAT), EuroQol-5 Dimensions, five-level version (EQ-5D-5L)] at 12 months post randomisation:
    a. The CAT score can range from 0 to 40, and the total score was used to compare between groups.
    b. The total score EQ-5D-5L was calculated using the mapping function developed by van Hout *et al.*[45] and the Crosswalk value sets for the UK; it ranges from − 0.594 to 1, with − 0594 indicates unable to/extreme problems on all of the five dimensions, and 1 indicates no problems on any of the five dimensions.
11. Antibiotic resistance (determined by sputum culture at baseline, all AECOPD and 12 months).
12. Health resource usage (HRU); self-reported by participant every 3 months, and submitted using a specific HRU CRF (at 3, 6, 9 and 12 months post randomisation, respectively).

After the early termination of the trial, the self-reported AECOPD, the QoL outcomes (EQ-5D-5L and CAT) were not obtained repeatedly every 3 months but only at 12 months post randomisation, and hence results from the self-reported AECOPD obtained by telephone calls to patients every 3 months were not reported. The EQ-5D-5L total score and the HRU outcomes were meant to be assessed in the economic evaluation; however, after trial cessation was recommended by NIHR, this analysis was discontinued, in order to maximise return to the NIHR and because data were limited. Additionally, the self-reported AECOPD analysis was limited to the data obtained at 12 months.

Sample size and trial duration considerations

We used hospitalisation rates from the Clinical Practice Research Datalink (CPRD) to determine event rate for our primary outcome.[29] Assuming a one-sided significance level of 2.5% and a rate of admission in each group of 65% of that in the referenced data, with a non-inferiority margin of 6% points, we would need to enrol 1329 patients in each of the intervention and control groups (2658 in total) to have 90% power for determining whether the results in the usual-care group were non-inferior to those in the intervention group. Assuming dropout/lost to follow-up/non-adherence rate of 10%, we therefore needed to recruit 2954 patients. We selected the 6% non-inferiority margin on the basis of clinical judgment that this was a reasonable threshold for a trade-off between a decrease in hospital admissions and other desired outcomes (reduced antibiotic use and resistance) while also being feasible to recruit to relatively quickly. To show

non-inferiority, the two-sided 95% confidence interval (CI) of the difference between hospitalisation rates should not exceed the pre-specified non-inferiority margin of 6%; the significance level set for this non-inferiority test was set at 0.025 (one-sided). A 5% or 4% non-inferiority threshold would require > 4200 and > 6500 patients, respectively; these margins necessitated large numbers of sites which lowered feasibility unless trial duration was extended. This was undesirable, as changes in COPD management and/or health service design might affect our outcomes. With our chosen non-inferiority threshold, we required around 80 GP practices, assuming that we target larger practices whose list sizes are likely to have > 70 eligible patients, and thus around 35 recruits.

A systematic review of non-inferiority studies, as well as a textbook of sample sizes for clinical trials, suggest that a one-sided test is the appropriate one to use in a study design with a clear hypothesis.[46,47] In this case, we did not believe our intervention could be better than the standard arm with respect to hospital admissions (which was the primary outcome specified by the brief) because data from our own systematic review of SM in COPD have not shown any association between such interventions and reduced admission rates[19]; consequently, we hypothesised that the two arms would not differ in their admission rates. A non-inferiority design allowed us power appropriately to assess safety – it remained possible that use of a colour chart would prompt patients to take less treatment than usual care, and this has potential to increase admissions if done inappropriately for the clinical setting.

The CPRD data also showed that these GOLD C and D patients comprise nearly 46% of registered COPD patients in primary care, indicating that this should not limit recruitment. Changing definitions of COPD severity within GOLD, specifically the removal of FEV1 percentage, predicted as a severity criterion, had potential to alter this prevalence; however, in UK data, the proportions did not appear to change markedly when using AECOPD rate instead of spirometry to determine severity.[29] We also consulted the national COPD audit to verify data on admission rates in the period after a hospitalisation;[48] the most recent report included data from 183 hospitals and 13,414 patients in England and Wales, and the rates indicated a similar risk to the CPRD data such that we were confident in the veracity of the data with respect to the whole UK. This indicated at trial design stage that we should be able to complete recruitment in 2 years. However, the pandemic impacted recruitment and ultimately meant the study was not able to recruit to target.

Randomisation

Participants were randomised by computer (or telephone if practices had poor online access) at the level of the individual in a 1 : 1 ratio to either 5-point sputum colour chart, adapted from Bronkotest colour chart or usual care as described previously, by the BCTU team. A minimisation algorithm was used within the online randomisation system to ensure balance in the treatment allocation over the following variables, which centre on factors influencing AECOPD and admission:

- severity of COPD[4]
  - C: CAT < 10, 2 or more exacerbations in the last 12 months OR ≥ 1 hospital admission for an exacerbation
  - D: CAT ≥ 10, 2 or more exacerbations in the last 12 months OR ≥ 1 hospital admission for an exacerbation
- presence or absence of chronic bronchitis
- prior COPD hospitalisation (yes or no within the 12 months prior to enrolment)
- age, as defined by < 65 years, 65–80 years, > 80 years.

In addition, GP practice was included to balance for effect of this. A 'random element' was included in the minimisation algorithm, so that each participant has a probability (unspecified here), of being randomised to the opposite treatment that they would have otherwise received.

Data collection

For Appointment 1 (screening) and Appointment 2 (12-month follow-up), one of the following four delivery methods were used (in order of preference, and to cover all eventualities):

1. face to face
2. video consultation
3. telephone with video links sent via e-mail to all parties to assist with the delivery of the intervention, that is, instructions on how to use the SM plan ± sputum colour chart
4. telephone only (with written instructions posted to intervention participants).

Screening/Appointment 1

Informed consent was taken prior to any study assessments being conducted. Appointment 1 was similar to the normal annual COPD review. It included assessment of inclusion/exclusion criteria, a review of medical history

and concomitant medication, completion of CAT and EQ-5D-5L questionnaires, MRC score and lung function measurements (FEV1 and FVC), and randomisation to either intervention or best usual care. Where this appointment took place remotely via telephone or online video link, the CAT and EQ-5D-5L questionnaires and MRC score were completed by reading the questions to the patient and recording their response.

Telephone calls

A telephone call was made to the participant by the research team at 2 weeks, 3 months, 6 months and 9 months from Appointment 1, with the purpose of assessing fidelity of the intervention (2 weeks), prospectively collecting data on AECOPD rate and improving retention (all other calls). Adverse events were recorded and the CAT and EQ-5D-5L questionnaires = completed by reading the questions to the patient and recording their response. At 6 months, two short questionnaires measuring self-efficacy were also completed: Patient-Reported Outcomes Measurement Information System (PROMIS) 'General Self-Efficacy – Short Form 4a' and PROMIS 'Self-Efficacy for Managing Chronic Conditions – Managing Medications and Treatment – Short Form 8a'. However, early cessation of the study and our closedown plan minimising cost to the NIHR removed 3-, 6- and 9-month calls and the PROMIS questionnaire from the protocol, to enable more budget return to the NIHR.

Appointment 2

Appointment 2 took place 12 months after enrolment and was like Appointment 1; CAT and EQ-5D-5L questionnaires were completed. Smoking status, concomitant medication, MRC score, lung function measurements (FEV1 and FVC), AECOPD and adverse events were recorded.

Self-reported AECOPD were compared to that confirmed in the medical record; however, the medically confirmed value was assumed as the true number for the purpose of our secondary outcome analysis of AECOPD rate and would have been used in subsequent economic evaluation.

Statistical analysis

All primary analyses (primary and secondary outcomes, including safety outcomes) were by intention to treat (ITT). Participants were analysed in the intervention group to which they were randomised, and all participants were included whether or not they received the allocated intervention. This is to avoid any potential bias in the analysis. Further supportive/sensitivity analyses, such as per-protocol analysis or subgroup analysis, were planned but were not conducted, as the trial was stopped early and data are insufficient to perform analyses. Results are displayed as estimates and 95% CIs derived from appropriate log-binomial regression model/generalised linear models. For all outcome measures, appropriate summary statistics are presented by intervention group (frequency count and percentages for categorical data, mean and standard deviation for continuous data). Intervention effects were adjusted for the minimisation variables where possible. No adjustment for multiple comparisons was made.

Primary outcome measure

For the analysis of the primary outcome measure, frequencies and percentages by group summarise the number of participants who had at least one hospital admission due to an AECOPD, and a log-binomial model was used to estimate a risk ratio (RR) and a risk difference (RD) along with their 95% CIs. Adjusted comparisons taking into account all minimisation variables, apart from GP practice, were performed but resulted to convergence issues and thus were not used. Further analyses of the episodes of AECOPD over 12 months using generalised estimating equations were considered in our plan, but not done due to early cessation. Non-inferiority statistics were not considered due to early cessation.

Secondary outcome measures

Self-reported antibiotic for AECOPD and all-cause steroid prescriptions at 12 months post randomisation

Number of participants who reported at least one prescription for antibiotic due to an AECOPD was summarised using frequencies and percentages by group and analysed as per the primary outcome, with the only difference that adjusted comparisons taking into account all minimisation variables, apart from GP practice, were performed because they did not result to convergence issues. Total number of antibiotic prescriptions due to an AECOPD per participant is reported alongside an adjusted incidence rate ratio (IRR) (and corresponding 95% CI) estimated using a negative binomial regression model instead of a Poisson regression model because there was evidence of overdispersion, adjusting for the minimisation variables as before. The natural logarithm of time in years from the date of randomisation to the date of trial last appointment was added as an offset variable to incorporating exposure time. Number of participants who reported at least one prescription for steroid was analysed in a similar way.

All-cause hospital admission/self-reported prescriptions for second courses of antibiotics within 14 days of self-reported event (defined as treatment failure)/ antifungals prescriptions, participant self-report at 12 months post randomisation

These outcomes were treated as binary outcomes, and Poisson regression models with robust error variance were used due to convergence issues to estimate an adjusted relative risk (aRR) (and corresponding 95% CI), taking into account all minimisation variables, apart from GP practice. In these cases, to estimate the adjusted risk differences (aRDs) (and corresponding 95% CI), logistic regression models with robust standard errors were employed, followed by the standardisation approach for covariate adjustment.

Bed-days due to AECOPD at 12 months post randomisation

Total number of bed-days due to an AECOPD per participant among those who had at least one hospital admission were presented only descriptively and summarised by group using medians and interquartile ranges (IQRs) per group because data were skewed.

Mortality, as determined by the medical record at 12 months post randomisation

Mortality was planned to be analysed using Kaplan–Meier curves with log rank test, and Cox regression models were fitted to obtain hazard ratios (and corresponding 95% CIs) estimated, adjusting for minimisation variables as before. Date of censoring for survival analyses was the date of either withdrawal, lost to follow-up or the exact date, whichever occurs first. Since the mortality rate was observed to be low, mortality is presented only descriptively and summarised by group using frequencies and percentages.

Re-admission to hospital for AECOPD (30 days)/re-admission to hospital for AECOPD (90 days), participant self-report at 12 months post randomisation

These outcomes were treated as binary outcomes, and the number of participants who reported at least one re-admission to hospital for AECOPD within 30/90 days was summarised using frequencies and percentages, but further analyses were not performed due to lack of events.

Quality of life (COPD assessment test, EuroQol-5 Dimensions, five-level version] at 12 months post randomisation

The total CAT and EQ-5D-5L scores at 12 months post randomisation were analysed individually using a linear regression model adjusting for baseline total scores and minimisation variables, apart from GP practice as before. Means and standard deviations were reported alongside adjusted mean differences (with the corresponding 95% CIs). The EQ VAS score is presented descriptively and summarised by group using means and standard deviations per group.

Health resource usage

The HRU outcomes were meant to be assessed in the economic evaluation; however, after trial cessation was recommended by NIHR, this analysis was discontinued, in order to maximise return to the NIHR and because data were limited.

Sputum substudy

Data collection

Subjects consented to the substudy were asked to send a sputum sample at baseline, 12-month follow-up and during any exacerbation. Subjects completed a sputum receipt form, which requested information on date and time of sample expectoration, contents of RP medication and the colour of their sputum. Intervention subjects were also asked to report their sputum colour according to the 5-point Bronkotest. Samples were posted, by subjects, using Royal Mail SafeBox™ First Class service and were received at the University of Birmingham Research Laboratories at the University Hospitals Birmingham site. Upon receipt, the sputum colour and weight was recorded by laboratory personnel. About 0.2 g of sample was diluted at 1 : 1 ratio with dithiothreitol (DTT) and stored at −80 °C for further microbiome analysis at a later date. Where sufficient sample was remaining (a minimum of 0.4 g), quantitative culture was performed. Sputum was diluted at a 1 : 1 ratio with DTT and incubated at room temperature for 15 minutes. The sample was then serially diluted, in sterile 0.9% sodium chloride, to give 10–3, 10–4 and 10–5 concentrations. About 10 ml of each dilution was plated on Columbia Chocolate Agar with 5% Horse Blood (Scientific Laboratory Supplies Ltd, Nottingham, UK). About 10 ml of 10–4 dilution was also plated on Columbia Agar with 5% Horse Blood (Scientific Laboratory Supplies, Nottingham, UK). Where insufficient sputum weight was available for quantitative culture, a primary streak plate was performed using a single loop full of sputum. Agar plates were incubated for 24–48 hours in 5% CO_2 at 37 °C. The morphology of bacterial isolates was examined, and, where a potentially pathogenic bacterium (PPB) was suspected, an initial Gram stain was performed. The Gram status and shape of bacteria were used to dictate subsequent biochemical identification tests.

Where a PPB was confirmed, antibiotic sensitivity was performed. A bacterial suspension was prepared by

inoculating 1 ml sterile phosphate-buffered saline with two to three colonies. Using a sterile swab, the inoculum was spread equally across the surface of a nutrient agar plate. For *Haemophilus* and *Moraxella* species, Iso-Sensitest Agar with Horse Blood and 20 mg/l NAD (Fisher Scientific Ltd, Leicester, UK) was used. Antibiotic discs, impregnated with 30 mg amoxicillin/clavulanic acid, 10 mg ciprofloxacin and 30 mg doxycycline (Oxoid Ltd, Reading, UK), were placed equidistantly on the agar. Plates were incubated, as described above, and zones of inhibition were measured for each disc to determine antibiotic susceptibility.

E-diary substudy

Data collection

A substudy compared self-reported AECOPD in 'real-time' between the two study arms using an e-diary among patients who had suitable devices and agreed to take part. While daily diaries can be done on paper, they are most reliable and cost-effective when done electronically.[49] Our e-diary assessed AECOPD using the EXACT score, symptoms and Anthonisen types of AECOPD.[5] The EXACT score reliably detects AECOPD.[50] E-diary data therefore described unreported (untreated) AECOPD rates as well as treated events, and potentially could have enhanced power to detect AECOPD rate if these events are numerous. Furthermore, it would have provided additional data on patient behaviour with respect to antibiotic use in relation to daily symptoms (e.g. whether they are taken in a timely manner relative to symptom changes). The EXACT score does not ask about change in sputum colour; we therefore asked this as an additional question (separate to the EXACT 14-item questionnaire so scoring is unaffected). Intervention participants were asked on the e-diary if they have noticed a change in their sputum colour and what number on their sputum chart represents their sputum colour. They received a colour chart to use alongside this question, provided on a card (as for the whole intervention group) and the colours numbered to ensure that screen settings did not affect interpretation of colour by the patient.

E-diary users were enrolled consecutively from the start, randomising as usual, aiming for $n = 300$ (10% of the total). Patients were approached about the substudy at Appointment 1, and, if eligible, informed consent was obtained. They were asked to complete the e-diary daily; estimated time to complete each day was 3 minutes. Data were linked to a pseudo anonymous patient identifier.

Data analysis

All e-diary data were analysed independent of additional data collection to avoid bias on recognition of exacerbations. Baseline patient demographics of those patients enrolled in the e-diary substudy and exacerbations features were summarised; means ± standard deviation (SD) were used for normally distributed continuous variables, and medians (IQR) for non-normal continuous variables. Frequency and percentages were used for categorical variables. Follow-up was calculated from the first entry to final entry chronologically, with data missingness calculated as all missing values in between these dates.

The e-diary symptom score was calculated from the individual daily responses and compared graphically on an individual basis. Exacerbation episodes were assessed from 14 days before and to 14 days after the start date of an exacerbation. A respiratory clinician assessed the daily responses to determine if an exacerbation was likely to have occurred, including whether this was treated with antibiotics and/or prednisolone to identify untreated as well as reported (treated) exacerbations. A proportion of entries were cross-checked against that of another respiratory doctor to ensure agreement. Exacerbation episodes were assessed graphically individually and by mean score across the entire cohort, with means and standard errors of the mean calculated. These scores were then stratified for treated versus untreated exacerbations. Low numbers of participants meant that planned analyses about whether SM was conducted meaningfully and promptly were not conducted, as no conclusions could be drawn.

Qualitative substudy

This substudy dealt with acceptability of the intervention, and aspects of process evaluation, including programme reach. For the latter, all those declining to participate in the trial were invited to complete a very brief questionnaire online or over the phone, without storing any identifiable data. Details of methods and results for the acceptability aspect of the substudy are in the threaded publication published by the journal *npj Primary Care Respiratory Medicine*.[51]

Multiple long-term conditions

Our exploratory objective pertaining to multiple long-term conditions (MLTCs) planned on mixed-methods analysis, incorporating exploration of the difficulties patients might experience in differentiating exacerbations of comorbid conditions from COPD and whether they experienced SM differently in the qualitative process evaluation. The original sample size for the qualitative substudy was expanded to allow the MLTC work to be conducted. Patients participating

in the Colour-COPD trial who had consented to being contacted about the qualitative substudy were purposively sampled to include a range of MLTCs. These patients were invited to participate in interviews with the qualitative team. The topic guide for the qualitative substudy was developed to explore issues of symptom interpretation, confidence in SM and use of healthcare providers during exacerbation events and barriers to participation in trials for those with MLTCs, and whether tailored approaches might aid recruitment and follow-up in studies of SM.

Participants were contacted from different parts of England and sampled to promote maximum variation of sociodemographic characteristics, trial arm and frequency of AECOPD. Some patients were invited to participate in follow-up interviews. Interviews were audio-recorded, transcribed verbatim, then analysed thematically, using an adapted Framework approach.[52] Expert patients (KA and SS) were recruited to contribute to the analysis of the patient data.

Results

Recruitment: lessons learnt

The study gained ethics and Health Research Authority (HRA) approval on 4 November 2020, and the first site opened on 11 November 2021. This reflects the delays inherent in adapting the protocol to enable it to run at all within the rules in place for social and medical contact in the early stages of the COVID-19 pandemic, as well as the multiple delays in site opening due to diversion of staff into other duties. The main issues thereafter were, firstly, primary care capacity was a major barrier nationwide. The trial was designed to be aligned with usual care; however, this was not happening in a reliable manner, which meant that many primary care sites did not see the trial population at the frequency we had anticipated. To overcome this issue, we started to implement a dual recruitment strategy, with both primary and secondary care sites open to recruitment, and this had seen recruitment numbers grow, as the secondary care pathway was well aligned with usual care. Secondly, AECOPD rates fell across the world[53] as patients isolated themselves and picked up fewer infections; this reduced eligibility because of fewer frequent exacerbators being in the UK population than expected.

The third issue was that our local Clinical Research Network (CRN) processes and logistics had created a barrier to recruitment. Initially the CRN had requested we open one site at a time to allow for learning to be cascaded; however, they were unable to find any sites willing to sign up for the trial. We then went to CRNs outside of our local area; however, lags continued due to creation of search strategies for GPs being delayed by the CRN. This meant that we were missing many potential participants from mail-outs about the study. Eventually, search strategies were created and six regions actively recruited for the trial, but this was too late to meet our pilot objectives regarding recruitment, hence why closure was mandated by the NIHR in November 2022. We developed more robust training for active sites to support them with recruitment and follow-up; issued monthly newsletters, including tips and 'prizes' for best performing sites; and conducted monthly drop-in support meetings online, but capacity to engage with the study remained low, and we lost sites that had initially reached out to express an interest. The closedown plan included amendment to the protocol to remove assessments and reduce cost, and when these were approved, the study was closed down formally, with the last recruit occurring in March 2023, and follow-up occurring 12 months later. It is possible that some of these changes reduced learning; for example, we had planned video-recording of consultations to check fidelity of delivery even further, but this was not conducted due to the budget changes. Sites participating are listed in *Table 1* and rate of recruitment is shown in *Figure 4*.

We inquired with sites about barriers to the trial during the process evaluation, and in addition to the aspects reported above, they fed back that lack of access to spirometry following the pandemic prevented them from enrolling in some cases (when historic tests were not available), that there was a lack of space to see patients, while other clinics were running (especially during periods of social distancing) and that text messages (suggested by the lead CRN) did not really boost recruitment for this patient population. Some research nurses rang their patients in an attempt to boost recruitment; this was time-consuming and not very successful. Radio advertisements for the study were suggested in Salford, having been successful before, and less prone to digital exclusion (as compared to web-based or social media methods of direct-to-patient promotion) but are unlikely to be feasible to design for many studies.

The study flow chart is shown in *Figure 5*. Two deceased participants were included in the primary outcome because a serious adverse event (SAE) form reported a hospital admission due to a COPD before their date of death. One participant who withdrew was included in the primary outcome because a SAE form reported a hospital admission due to a COPD before the withdrawal date. One participant was considered as lost to follow-up only

TABLE 1 Recruitment at sites participating in Colour-COPD

	Colour chart, SM plan and RP (intervention)	SM plan and RP (best usual care)	Total
	N = 57	*N* = 58	*N* = 115
University Hospitals Birmingham NHS Foundation Trust	22 (39%)	19 (33%)	41 (36%)
North Cumbria Integrated Care	7 (12%)	7 (12%)	14 (12%)
Brierley Park Medical Centre	7 (12%)	4 (7%)	11 (10%)
Salford Royal Hospital	3 (5%)	6 (10%)	9 (8%)
College Green Medical Practice	3 (5%)	3 (5%)	6 (5%)
Bodey Medical Centre	2 (4%)	3 (5%)	5 (4%)
Middlewood Partnership	3 (5%)	2 (3%)	5 (4%)
Fearnhead Cross Medical Practice	2 (4%)	3 (5%)	5 (4%)
White Horse Medical Practice	2 (4%)	2 (3%)	4 (3%)
Queen Square Medical Practice	2 (4%)	1 (2%)	3 (3%)
Royal Primary Care Ashgate	1 (2%)	2 (3%)	3 (3%)
The Sides Medical Centre	0 (0%)	3 (5%)	3 (3%)
Hugglescote Surgery	0 (0%)	2 (3%)	2 (2%)
Windrush Medical Practice	1 (2%)	1 (2%)	2 (2%)
Barlow Medical Centre	1 (2%)	0 (0%)	1 (1%)
Church Street Practice	1 (2%)	0 (0%)	1 (1%)

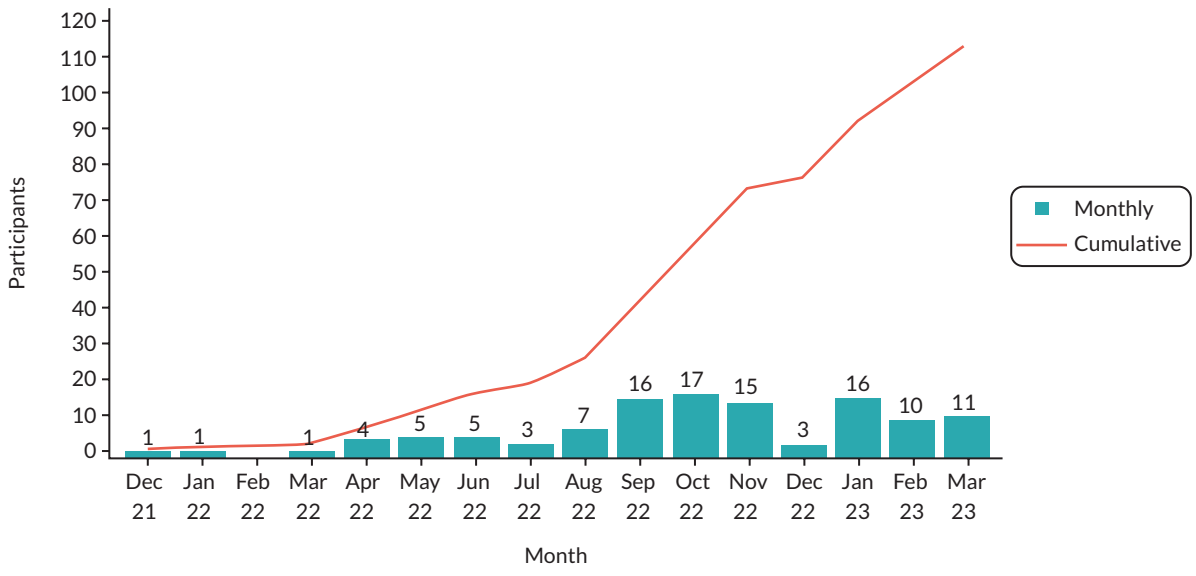

FIGURE 4 Number of randomised participants by month.

for the primary outcome as some secondary outcome data had been reported. One deceased participant was included in the primary outcome because a SAE form reported a hospital admission due to a COPD exacerbation before their date of death.

Patient characteristics

The characteristics of the participants in the study by group and overall can be seen in *Table 2*. The minimisation variables used in the randomisation as are listed first. General practice was also a minimisation variable. Groups

appeared well balanced at baseline. Comorbidity was common, with hypertension being present in almost half of participants, approximately 30% of patients having asthma, 25% bronchiectasis and 25% vascular disease (either coronary or cerebral). The majority of patients were not highly educated, and smoke exposure was heavy, though the majority had quit prior to enrolment. At follow-up, number of current smokers was lower in the colour chart group (3 vs. 12 in control). Eosinophil counts exhibited a wide range, but the mean was within normal parameters. Symptom and QoL scores indicated poorly controlled, symptomatic disease, driven by breathlessness. Most patients were taking regular triple therapy[long-acting muscarinic antagonist (LAMA)/long-acting beta 2 agonist (LABA)/inhaled corticosteroid (ICS)], half were also on mucolytics. Proportions of patients on other relevant treatments were mainly similar between arms except for oxygen and home ventilation, which were more common in the colour chart arm. Almost all patients used either amoxicillin or doxycycline in their RP.

Conduct of the trial

The return rate of the 12-month follow-up clinical form was more than 80% in both groups, whereas the return

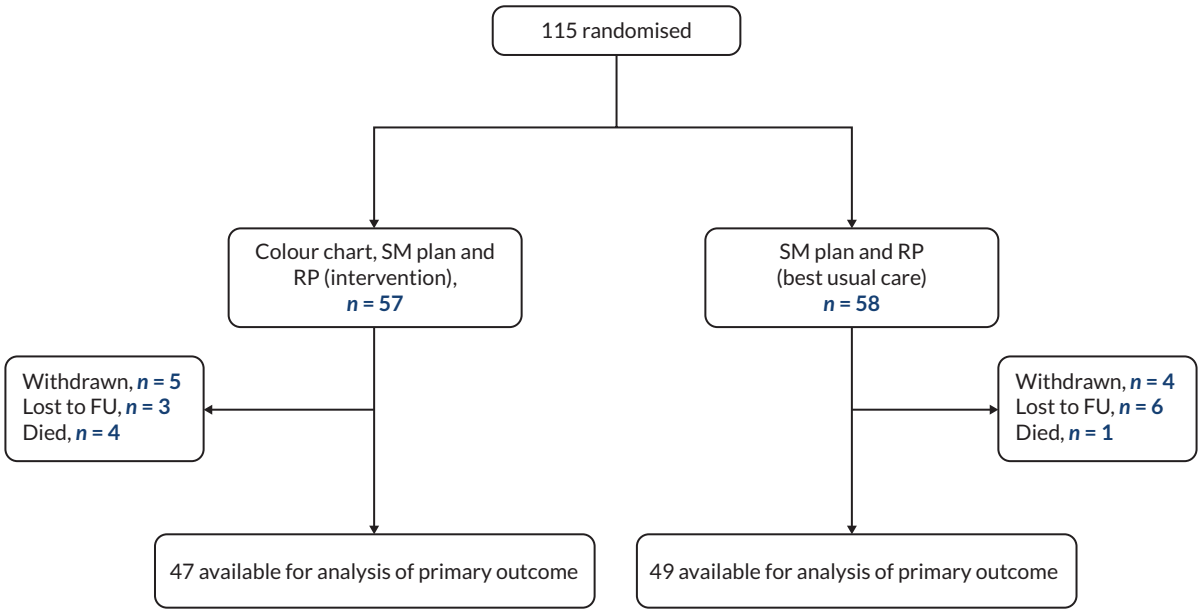

FIGURE 5 Consolidated Standards of Reporting Trials diagram.

TABLE 2 Baseline characteristics by group and overall

	Treatment allocation		
	Colour chart, SM plan and RP (intervention)	SM plan and RP (best usual care)	Total
	N = 57	*N* = 58	*N* = 115
Minimisation variables			
Severity of COPD, n (%)			
Category C[a]	4 (7%)	3 (5%)	7 (6%)
Category D[b]	53 (93%)	55 (95%)	108 (94%)
Presence of chronic bronchitis, n (%)			
Yes	32 (56%)	33 (57%)	65 (57%)
Prior COPD hospitalisations, n (%)			
Yes	20 (35%)	20 (34%)	40 (35%)

continued

TABLE 2 Baseline characteristics by group and overall (*continued*)

	Treatment allocation		
	Colour chart, SM plan and RP (intervention)	SM plan and RP (best usual care)	Total
	N = 57	*N* = 58	*N* = 115
Age groups (years), n (%)			
Age < 65	17 (30%)	17 (29%)	34 (30%)
65 ≤ age ≤ 80	33 (58%)	35 (60%)	68 (59%)
Age > 80	7 (12%)	6 (10%)	13 (11%)
Demographic and other baseline variables			
Age at randomisation (years)			
Mean (SD)	68.9 (9.2)	68.2 (9.1)	68.5 (9.1)
Gender, n (%)			
Male	29 (51%)	34 (59%)	63 (55%)
Female	28 (49%)	24 (41%)	52 (45%)
Ethnicity, n (%)			
White – British/English/Northern Irish/Scottish/Welsh	57 (100%)	56 (97%)	113 (98%)
Asian and Asian British – Indian	0 (0%)	1 (2%)	1 (1%)
Black and Black British – African Caribbean	0 (0%)	1 (2%)	1 (1%)
Body mass index (BMI) (kg/m^2)			
Mean (SD)	28.6 (7.8)	26.9 (5.9)	27.7 (6.9)
Education level, n (%)			
No formal education	19 (33%)	17 (29%)	36 (31%)
GCSE, CSE, O Level or equivalent	24 (42%)	24 (41%)	48 (42%)
A Level/AS Level or equivalent	6 (11%)	5 (9%)	11 (10%)
Degree level or higher	7 (12%)	6 (10%)	13 (11%)
Others (please specify)	1 (2%)	6 (10%)	7 (6%)
Medical history			
Number of hospitalisations for COPD in previous year			
None	37 (65%)	39 (67%)	76 (66%)
One	8 (14%)	14 (24%)	22 (19%)
Two	5 (9%)	1 (2%)	6 (5%)
Three	3 (5%)	0 (0%)	3 (3%)
More than three	4 (7%)	4 (7%)	8 (7%)
Number of participants who had a full blood count while stable within the last 12 months			
Yes	40 (71%)	44 (76%)	84 (74%)
Missing	1	0	1

TABLE 2 Baseline characteristics by group and overall (*continued*)

	Treatment allocation		
	Colour chart, SM plan and RP (intervention)	SM plan and RP (best usual care)	Total
	N = 57	*N* = 58	*N* = 115
Most recent eosinophil level			
Mean (SD)	0.18 (0.17)	0.20 (0.15)	0.19 (0.16)
Chronic asthma, n (%)			
Yes	17 (30%)	20 (34%)	37 (32%)
Bronchiectasis, n (%)			
Yes	10 (18%)	15 (26%)	25 (22%)
Medical history (ICD-10)			
Diabetes, n (%)			
Yes	13 (23%)	11 (19%)	24 (21%)
CVA/stroke/TIA, n (%)			
Yes	2 (4%)	4 (7%)	6 (5%)
Osteoporosis, n (%)			
Yes	11 (19%)	8 (14%)	19 (17%)
Hypertension, n (%)			
Yes	23 (40%)	30 (52%)	53 (46%)
Arthritis, n (%)			
Yes	20 (35%)	19 (33%)	39 (34%)
Coronary heart disease, n (%)			
Yes	9 (16%)	12 (21%)	21 (18%)
Depression/anxiety, n (%)			
Yes	21 (37%)	19 (33%)	40 (35%)
GORD, n (%)			
Yes	14 (25%)	17 (29%)	31 (27%)
Smoking status			
Current smoking status, n (%)			
Current smoker	10 (18%)	15 (26%)	25 (22%)
Ex-smoker	38 (67%)	40 (69%)	78 (68%)
Never smoked	9 (16%)	3 (5%)	12 (10%)
Duration of smoking (years)			
Mean (SD)	39.3 (13.3, 47)	38.5 (15.8)	38.9 (14.6)
Number of cigarettes/day			
Mean (SD)	18.2 (9.9)	17.4 (12.5)	17.8 (11.4)

continued

TABLE 2 Baseline characteristics by group and overall (*continued*)

	Treatment allocation		
	Colour chart, SM plan and RP (intervention)	SM plan and RP (best usual care)	Total
	N = 57	*N* = 58	*N* = 115
Medical measurement			
FEV1: Pre bronchodilator (litres)			
Mean (SD)	1.4 (0.7)	1.5 (0.5)	1.4 (0.6)
FEV1: Post bronchodilator (litres)			
Mean (SD)	1.6 (0.6)	1.5 (0.6)	1.5 (0.6)
MRC Breathlessness Scale, n (%)			
Grade 1	1 (2%)	2 (3%)	3 (3%)
Grade 2	9 (16%)	7 (12%)	16 (14%)
Grade 3	18 (32%)	16 (28%)	34 (30%)
Grade 4	16 (28%)	23 (40%)	39 (34%)
Grade 5	13 (23%)	10 (17%)	23 (20%)
Baseline CAT score[c]			
Mean (SD)	23.25 (8.65)	24.48 (7.75)	23.87 (8.19)
Baseline EQ-5D-5L score[d]			
Mean (SD)	0.55 (0.32)	0.56 (0.28)	0.55 (0.30)
Baseline EQ-5D-5L VAS score[e]			
Mean (SD)	55.4 (22.4)	58.4 (23.1)	56.9 (22.7)
Concomitant medication at baseline			
Nebulised drugs, n (%)			
No	42 (74%)	46 (79%)	88 (77%)
Yes	15 (26%)	12 (21%)	27 (23%)
Among those who take nebulised drugs			
Types of nebulised drug, n (%)			
Bronchodilators only	10 (67%)	8 (67%)	18 (67%)
Saline only	1 (7%)	0 (0%)	1 (4%)
Colomycin only	0 (0%)	1 (8%)	1 (4%)
Unknown	1 (7%)	0 (0%)	1 (4%)
Bronchodilators and saline	3 (20%)	3 (25%)	6 (22%)
Types of inhaled drug, n (%)			
LAMA	0 (0%)	1 (2%)	1 (1%)
LAMA/LABA	7 (13%)	4 (7%)	11 (10%)
LABA/ICS	6 (11%)	4 (7%)	10 (9%)
LAMA/LABA/ICS	40 (73%)	43 (77%)	83 (75%)

TABLE 2 Baseline characteristics by group and overall (*continued*)

	Treatment allocation		
	Colour chart, SM plan and RP (intervention)	SM plan and RP (best usual care)	Total
	N = 57	*N* = 58	*N* = 115
SABA	1 (2%)	3 (5%)	4 (4%)
ICS	1 (2%)	0 (0%)	1 (1%)
LABA	0 (0%)	1 (2%)	1 (1%)
Missing	1	0	1
Mucolytic, n (%)			
Yes	29 (51%)	26 (45%)	55 (48%)
Prophylactic antibiotic, n (%)			
Yes	7 (13%)	10 (18%)	17 (15%)
Theophylline, n (%)			
Yes	6 (11%)	7 (12%)	13 (11%)
Long-term oxygen therapy (LTOT), n (%)			
Yes	3 (5%)	0 (0%)	3 (3%)
Ambulatory oxygen, n (%)			
Yes	5 (9%)	4 (7%)	9 (8%)
Domiciliary non-invasive ventilation (NIV), n (%)			
Yes	5 (9%)	1 (2%)	6 (5%)
Doxycycline (content of RP), n (%)			
Yes	21 (37%)	27 (47%)	48 (42%)
Amoxicillin (content of RP), n (%)			
Yes	30 (53%)	25 (43%)	55 (48%)
Co-amoxiclav (content of RP), n (%)			
Yes	2 (4%)	6 (10%)	8 (7%)
Ciprofloxacin (content of RP), n (%)			
Yes	0 (0%)	2 (3%)	2 (2%)
Clarithromycin (content of RP), n (%)			
Yes	3 (5%)	2 (3%)	5 (4%)

CVA, cerebrovascular accident; TIA, transient ischaemic attack.
a CAT< 10, 2 or more exacerbations in the last 12 months OR one hospital admission for an exacerbation.
b CAT ≥ 10, 2 or more exacerbations in the last 12 months OR one hospital admission for an exacerbation.
c The CAT score can range from 0 to 40. Higher scores indicate that participants' COPD has a greater impact on their overall health and well-being.
d The total score EQ-5D-5L was calculated using the mapping function developed by Van Hout *et al.*[45] and the Crosswalk value sets for the UK; and it ranges from −0.594 to 1, with −0594 indicating unable to/extreme problems on all of the five dimensions, and 1 indicating no problems on any of the five dimensions.
e EQ-5D-5L VAS health state scores range from 0 to 100, where higher scores reflect better health.

rate of the health economics form was (79% in the intervention group and 83% in the best usual care arm). The eligibility and baseline form had a 100% return rate in both arms. There were 13 protocol deviations, 9 relating to late reporting of SAEs, and none deemed to have affected safety of patients or integrity of results. Additionally, one protocol deviation regarding the late reporting of a SAE for a hospital admission was requested to be completed by the site but was not completed due to time constraints.

We assessed fidelity of delivery of the intervention. Self-management was delivered consistently and reliably during the trial, and was largely similar between arms, with the possible exception that RP was issued more commonly in the control arm (93% vs. 83%), as shown in *Figure 6*.

Outcomes

Hospital admissions for AECOPD showed a strong trend towards being higher in the colour chart group compared to usual care [32 vs. 16%, relative risk 1.95 (0.92 to −4.18)], as shown in *Table 3*. Most patients did not experience an admission, and there were three recurrently admitted patients in the colour chart arm (*Figure 7*).

The characteristics of the participants who experienced at least one hospital admission due to AECOPD over 12 months post randomisation in the study by group and overall can be seen in *Table 4*.

Results of secondary outcome analyses are summarised in *Tables 5–7*. Risk ratios are presented in accordance with

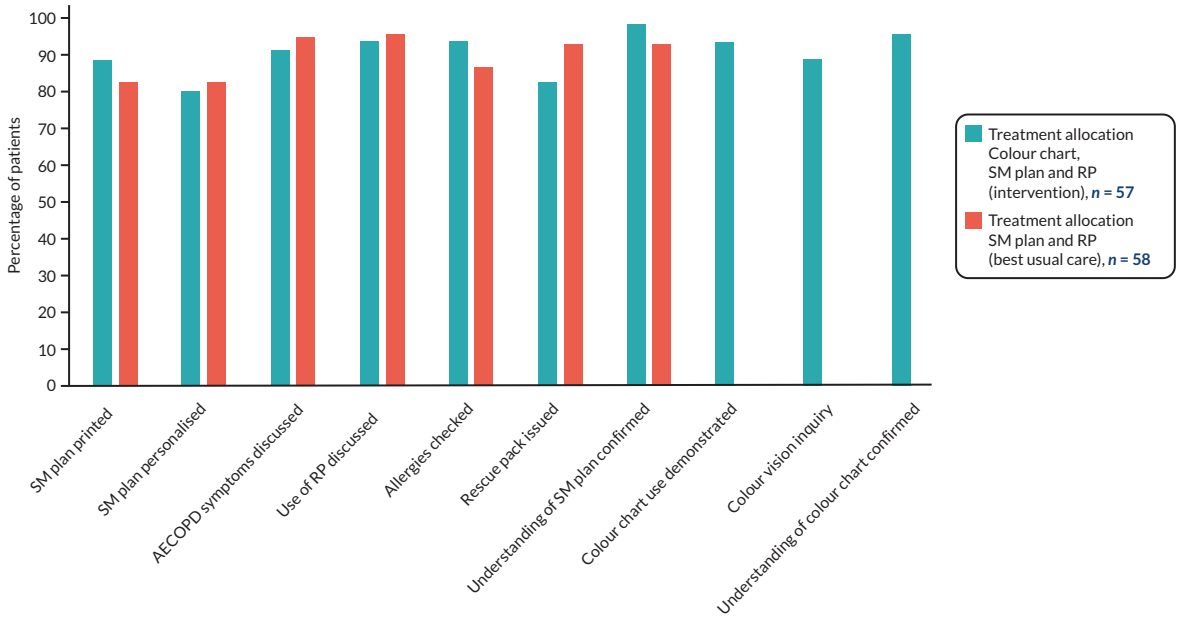

FIGURE 6 Delivery of key aspects of SM.

TABLE 3 Primary outcome summary statistics

Primary outcome		Allocated treatment: Colour chart, SM plan and RP (intervention) *N* = 57	Allocated treatment: SM plan and RP (best usual care) *N* = 58	Unadjusted relative risk[a,b,c] (95% CI)	Unadjusted risk difference[b,c,d] (95% CI)
Number of participants with at least one hospital admission due to AECOPD over 12 months post randomisation	Yes	15 (32%)	8 (16%)	1.95 (0.92 to 4.18)	0.16 (−0.01 to 0.32)
	No	32 (68%)	41 (84%)		
	Missing	10	9		

a RR < 1 favours the colour chart, SM plan and RP (intervention).
b Log-binomial regression model.
c Adjusted comparisons taking into account all minimisation variables, apart from GP practice, were performed but resulted to convergence issues and thus were not used.
d RD < 0 favours the colour chart, SM plan and RP (intervention).

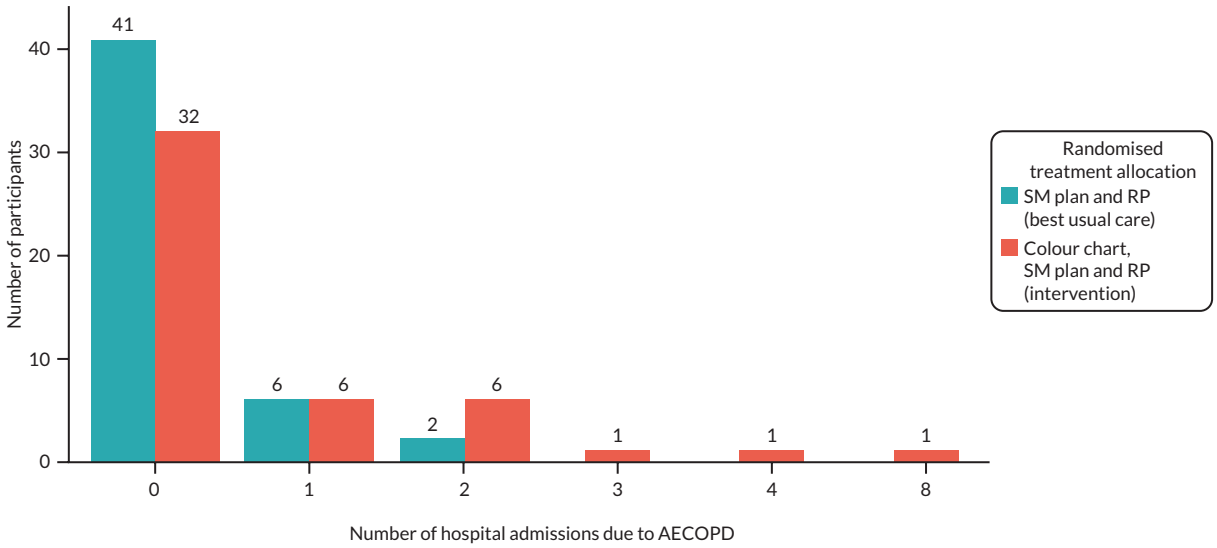

FIGURE 7 Number of hospital admissions per patient.

Consolidated Standards of Reporting Trials (CONSORT) requirements for reporting of trials, with adjusted risks shown, but all data, both numerical and adjusted, including CIs, must be interpreted very cautiously given the under-recruitment. Consistent with the primary outcome, re-admissions for AECOPD were higher in the colour chart group, and there were suggestive data for initial treatment failure in this group as well, with more second courses of antibiotics being used. General practitioner visits were rare for COPD in both arms. Counterintuitively, QoL (CAT score) was better at follow-up in the colour chart group, despite the hints towards worse outcomes from the healthcare utilisation data [19.9 vs. 24.5, adjusted mean difference −2.95 (−5.93 to −0.04)].

Safety

There were 51 SAEs. Of these, 34 were expected hospitalisations for AECOPD. The non-AECOPD SAEs were largely unexpected, and these are shown in *Table 8*. The reasons were consistent with the age, smoking profile and known literature regarding incidence of other diseases in COPD.

Sputum substudy

Thirty-eight patients were recruited to the sputum substudy of the Colour-COPD trial, of whom *n* = 19 were in the control group and *n* = 19 were in the intervention group (*Table 9*). The majority of patients were recruited from University Hospitals Birmingham NHS Foundation Trust (58%). Groups were matched for severity of COPD, prior COPD hospitalisations, age and sex. About 26% and 37% of the control and intervention group, respectively, had coexisting bronchiectasis. Most patients in both groups were ex-smokers at baseline (68% control group, 47% intervention), with 21% in each group still smoking; three patients in the intervention group stopped smoking during the study, compared to none in the control group. Most patients were very breathless – over half had MRC dyspnoea score ≥ 4 – and most had a low level of formal education, with 68% of both groups having been in education to age 16 or less. A total of 57 sputum samples were received from 37 patients (1 consented but did not submit a sample), of which 42 were collected during stable state disease and 15 during an exacerbation. Of the 37 patients, 26 provided one sputum sample, 8 patients provided two samples, 2 patients provided three samples, 1 patient provided four samples and 1 patient provided five samples.

As part of the sputum receipt form, patients were asked to list the contents of their RP medication. About 95% of patients had prednisolone as part of their RP. About 42% and 39% of RP contained amoxicillin and doxycycline, respectively. Co-amoxiclav, clarithromycin and ciprofloxacin were less common, prescribed in 13%, 5% and 3% RP, respectively.

Prevalence of potentially pathogenic bacteria

Of the 57 samples received, 17 (30%) were positive for a PPB. Thirty-six samples contained only mixed normal flora of the upper respiratory tract and a further four samples were missing lab receipt form data. About 10/42 (24%) stable samples were positive for a PPB, including 4 *Moraxella catarrhalis*, 3 *Pseudomonas* species, 2 *Haemophilus* influenzae and 1 *Staphylococcus aureus*. Of the 15 exacerbation samples, 7 were positive for a PPM (47%): 3 *M. catarrhalis*, 1 *Haemophilus* influenzae, 1 *Pseudomonas* spp. and 2 yeast.

TABLE 4 Baseline characteristics for individuals with exacerbations by group

	Treatment allocation		
	Colour chart, SM plan and RP (intervention)	SM plan and RP (best usual care)	Total
	N = 15	*N* = 8	*N* = 23
Minimisation variables			
Severity of COPD, n (%)			
Category D[a]	15 (100%)	8 (100%)	23 (100%)
Presence of chronic bronchitis, n (%)			
Yes	9 (60%)	7 (88%)	16 (70%)
Prior COPD hospitalisations, n (%)			
Yes	7 (47%)	5 (62%)	12 (52%)
Age groups (years), n (%)			
Age< 65	5 (33%)	6 (75%)	11 (48%)
65 ≤ age ≤ 80	9 (60%)	2 (25%)	11 (48%)
Age > 80	1 (7%)	0 (0%)	1 (4%)
GP (see *Table 2*)			
Demographic and other baseline variables			
Age at randomisation (years)			
Mean (SD, *N*)	68.16 (7.35, 15)	61.47 (8.19, 8)	65.83 (8.15, 23)
Gender, n (%)			
Male	5 (33%)	4 (50%)	9 (39%)
Female	10 (67%)	4 (50%)	14 (61%)
Ethnicity, n (%)			
White – British/English/Northern Irish/Scottish/Welsh	15 (100%)	7 (88%)	22 (96%)
Asian and Asian British – Indian	0 (0%)	1 (12%)	1 (4%)
BMI (kg/m²)			
Mean (SD, *N*)	27.74 (8.33, 15)	26.55 (4.99, 8)	27.33 (7.24, 23)
Education level, n (%)			
No formal education	8 (53%)	3 (38%)	11 (48%)
GCSE, CSE, O Level or equivalent	5 (33%)	4 (50%)	9 (39%)
A level/AS level or equivalent	1 (7%)	1 (12%)	2 (9%)
Degree level or higher	1 (7%)	0 (0%)	1 (4%)
Medical history			
Number of hospitalisations for COPD in previous year			
None	8 (53%)	3 (38%)	11 (48%)
One	2 (13%)	1 (12%)	3 (13%)

TABLE 4 Baseline characteristics for individuals with exacerbations by group (*continued*)

	Treatment allocation		
	Colour chart, SM plan and RP (intervention)	SM plan and RP (best usual care)	Total
	N = 15	*N* = 8	*N* = 23
Two	3 (20%)	1 (12%)	4 (17%)
More than three	2 (13%)	3 (38%)	5 (22%)
Has the participant had a full blood count while stable within the last 12 months?			
Yes	10 (71%)	7 (88%)	17 (77%)
Missing	1	0	1
Most recent eosinophil count			
Mean (SD, *N*)	0.19 (0.14, 10)	0.20 (0.14, 7)	0.20 (0.14, 17)
Chronic asthma, n (%)			
Yes	4 (27%)	3 (38%)	7 (30%)
Bronchiectasis, n (%)			
Yes	4 (27%)	1 (12%)	5 (22%)
Medical history (ICD-10)			
Diabetes, n (%)			
Yes	3 (20%)	2 (25%)	5 (22%)
CVA/stroke/TIA, n (%)			
Yes	1 (7%)	1 (12%)	2 (9%)
Osteoporosis, n (%)			
Yes	4 (27%)	1 (12%)	5 (22%)
Hypertension, n (%)			
Yes	6 (40%)	7 (88%)	13 (57%)
Arthritis, n (%)			
Yes	4 (27%)	2 (25%)	6 (26%)
Coronary heart disease, n (%)			
Yes	3 (20%)	1 (12%)	4 (17%)
Depression/anxiety, n (%)			
Yes	7 (47%)	3 (38%)	10 (43%)
GORD, n (%)			
Yes	3 (20%)	3 (38%)	6 (26%)
IBS, n (%)			
Yes	2 (13%)	1 (12%)	3 (13%)
OSA, n (%)			
Yes	0 (0%)	2 (25%)	2 (9%)

continued

This synopsis should be referenced as follows:
Gkini E, Adams RL, Spittle D, Ellis P, Allsopp K, Saleem S, *et al.* Sputum colour charts to guide antibiotic self-treatment of acute exacerbation of chronic obstructive pulmonary disease: the Colour-COPD RCT. [published online ahead of print May 21 2025]. *Health Technol Assess* 2025. https://doi.org/10.3310/KPFD5558

TABLE 4 Baseline characteristics for individuals with exacerbations by group (*continued*)

	Treatment allocation		
	Colour chart, SM plan and RP (intervention)	SM plan and RP (best usual care)	Total
	N = 15	*N* = 8	*N* = 23
Smoking status			
Current smoking status, n (%)			
Current smoker	4 (27%)	2 (25%)	6 (26%)
Ex-smoker	10 (67%)	5 (62%)	15 (65%)
Never smoked	1 (7%)	1 (12%)	2 (9%)
Duration of smoking (years)			
Mean (SD, *N*)	43.08 (7.84, 13)	45.71 (13.06, 7)	44.00 (9.71, 20)
Medical measurement			
FEV1: Pre bronchodilator (litres)			
Mean (SD, *N*)	0.82 (0.33, 8)	1.17 (0.41, 4)	0.94 (0.38, 12)
FEV1: Post bronchodilator (litres)			
Mean (SD, *N*)	1.55 (0.88, 6)	1.18 (0.49, 5)	1.38 (0.72, 11)
MRC Breathlessness Scale, n (%)			
Grade 2	1 (7%)	0 (0%)	1 (4%)
Grade 3	2 (13%)	1 (12%)	3 (13%)
Grade 4	5 (33%)	2 (25%)	7 (30%)
Grade 5	7 (47%)	5 (62%)	12 (52%)
CAT baseline score[b]			
Mean (SD, *N*)	29.53 (5.49, 15)	30.00 (6.95, 8)	29.70 (5.88, 23)
EQ-5D-5L baseline score[c]			
Mean (SD, *N*)	0.33 (0.36, 15)	0.31 (0.38, 8)	0.32 (0.36, 23)

a CAT ≥ 10, 2 or more exacerbations in the last 12 months OR one hospital admission for an exacerbation.
b The CAT score can range from 0 to 40. Higher scores indicate that participants' COPD has a greater impact on their overall health and well-being.
c The total score EQ-5D-5L was calculated using the mapping function developed by Van Hout *et al.*[45] and the Crosswalk value sets for the UK; and it ranges from −0.594 to 1, with −0594 indicating unable to/extreme problems on all of the five dimensions, and 1 indicating no problems on any of the five dimensions.

Patient-reported sputum colour was available for 54/58 samples received and was similar to the colour reported by lab personnel (p = 0.8). In the intervention group, patient-reported colour was similar to the associated number reported from the colour chart (p = 0.7). Sputum colour was more likely to be purulent (3–5 on colour chart) in subjects with bronchiectasis, independent of disease state (stable vs. exacerbation) or whether the sample was positive for a PPB (*Table 10*).

Multiple logistic regression model displaying odds of purulent samples during exacerbation, when positive for a PPB and in those with coexisting bronchiectasis. Intercept (95% CI) = 0.68 (0.28 to 1.58).

Antibiotic sensitivity was performed on 13 bacterial isolates. About 4/13 (31%) isolates displayed resistance to at least one antibiotic. About two-fourth instances of resistance were to amoxicillin/clavulanic acid (one

TABLE 5 Binary secondary outcome summary statistics

Binary secondary outcomes at 12 months		Allocated treatment: Colour chart, SM plan and RP (intervention) *N* = 57	Allocated treatment: SM plan and RP (best usual care) *N* = 58	Adjusted relative risk[a,b,c] (95% CI)	Adjusted risk difference[b,c,d] (95% CI)
Number of participants with at least one antibiotic prescription for AECOPD	Yes/*n*	37/46 (80%)	43/50 (86%)	0.98 (0.82 to 1.16)	−0.02 (−0.17 to 0.12)
Number of participants with at least one steroid prescription	Yes/*n*	38/46 (83%)	42/50 (84%)	1.02 (0.86 to 1.20)	0.01 (−0.13 to 0.15)
Number of participants with at least one all-cause hospital admission	Yes/*n*	19/50 (40%)	14/49 (29%)	1.47 (0.85 to 2.54)[e]	0.11 (−0.07 to 0.29)[f]
Number of participants with at least one prescription for second course of antibiotics for AECOPD within 14 days	Yes/*n*	15/44 (34%)	8/44 (18%)	1.80 (0.85 to 3.79)[e]	0.15 (−0.03 to 0.33)[f]
Number of participants with at least one prescription for antifungals (e.g. for oral thrush)	Yes/*n*	6/45 (13%)	5/48 (10%)	1.19 (0.37 to 3.89)[e]	0.02 (−0.11 to 0.16)[f]
Number of participants with at least one re-admission to hospital for AECOPD at 30 days	Yes/*n*	3/47 (6%)	0/49 (0%)	Analysis was not performed due to lack of events	
Number of participants with at least one re-admission to hospital for AECOPD at 90 days	Yes/*n*	4/47 (8%)	0/49 (0%)	Analysis was not performed due to lack of events	

a aRR < 1 favours the colour chart, SM plan and RP (intervention).
b Log-binomial regression model.
c Adjusted comparisons taking into account all minimisation variables apart from GP practice. Severity of COPD and presence or absence of chronic bronchitis were included as fixed effects; and age at randomisation and number of hospitalisations for COPD in previous year were included as continuous variables.
d aRD < 0 favours the colour chart, SM plan and RP (intervention).
e Instead of a log-binomial regression model, a Poisson regression model with robust error variance was used due to convergence issues.
f Instead of a binomial regression model with identity link function, a logistic regression model with robust standards errors was used, followed by the standardisation approach for covariate adjustment.

TABLE 6 Count-based secondary outcome summary statistics

Count secondary outcomes at 12 months		Allocated treatment: Colour chart, SM plan and RP (intervention) *N* = 57	Allocated treatment: SM plan and RP (best usual care) *N* = 58	Adjusted IRR[a,b,c] (95% CI)
Total number of antibiotic prescriptions due to AECOPD per participant[c]	Median [*n*, IQR]	2 [47, 1–4]	3 [52, 1–4]	1.03[d] (0.73 to 1.43)
Total number of GP visits due to COPD	Median [*n*, IQR]	2 [46, 0–5]	1 [51, 0–4]	1.28[e] (0.69 to 2.39)

a aIRR< 1 favours the colour chart, SM plan and RP.
b Adjusted comparisons taking into account all minimisation variables apart from GP practice. Severity of COPD and presence or absence of chronic bronchitis were included as fixed effects; and age at randomisation and number of hospitalisations for COPD in previous year were included as continuous variables.
c Three participants, for whom the binary outcome: number of participants with at least one antibiotic prescription for AECOPD was missing because they were not followed up for 12 months were included in the outcome: total number of antibiotic prescriptions due to AECOPD per participant until the time point they were followed up.
d Because there was evidence of overdispersion, it was considered more appropriate to use a negative binomial regression model. Dispersion parameter (95% CI) = 0.32 (0.17 to 0.62) with *p*-value < 0.001 according to the likelihood ratio (LR) test.
e Because there was evidence of overdispersion, it was considered more appropriate to use a negative binomial regression model. Dispersion parameter (95% CI) = 1.81 (1.19 to 2.75) with *p*-value < 0.001 according to the LR test.

TABLE 7 Continuous secondary outcomes summary statistics

Continuous secondary outcomes at 12 months		Allocated treatment		
		Colour chart, SM plan and RP (intervention) *N* = 57	SM plan and RP (best usual care) *N* = 58	Adjusted mean difference[a] (95% CI)
Total CAT score[b,c]	Mean (*n*, SD)	19.9 (30, 8.4)	24.5 (35, 6.0)	−2.95 (−5.93 to −0.04)
Total EQ-5D-5L score[d,e]	Mean (*n*, SD)	0.57 (27, 0.30)	0.54 (33, 0.24)	0.06 (−0.09 to 0.15)
EQ-5D-5L VAS score[f]	Mean (*n*, SD)	49.0 (26, 22.8)	56.1 (32, 22.9)	N/A
Bed-days due to AECOPD[g]	Number of participants ≥ 1 hospitalisation for AECOPD	15	8	
	Median [*n*[h], IQR]	7.0 [55, 6.0–12.0]	6.5 [56, 5.0–15.0]	N/A

a Adjusted mean difference < 0 favours the colour chart, SM plan and RP (intervention).
b Adjusted comparisons taking into account all minimisation variables apart from GP practice. Severity of COPD and presence or absence of chronic bronchitis were included as fixed effects; and age at randomisation, number of hospitalisations for COPD in previous year and baseline CAT score were included as continuous variables.
c The CAT score can range from 0 to 40. Higher scores indicate that participants' COPD has a greater impact on their overall health and well-being.
d The total score EQ-5D-5L was calculated using the mapping function developed by Van Hout *et al.*[45] and the Crosswalk value sets for the UK; and it ranges from −0.594 to 1, with −0594 indicating unable to/extreme problems on all of the five dimensions, and 1 indicating no problems on any of the five dimensions.
e Adjusted comparisons taking into account all minimisation variables apart from GP practice. Severity of COPD and presence or absence of chronic bronchitis were included as fixed effects; and age at randomisation, number of hospitalisations for COPD in previous year and baseline EQ-5D-5L score were included as continuous variables.
f EQ-5D-5L VAS health state scores range from 0 to 100, where higher scores reflect better health.
g Among those who had at least one hospital admission due to AECOPD.
h Four participants who were included in the primary outcome because they reported at least one hospital admission due to an AECOPD were not included in the bed-days outcome because this detail was not collected on the SAE form.

TABLE 8 Serious adverse events

Summary of SAE	Severity	Life-threatening	Relatedness	Expectedness
Colour chart, SM plan and RP (intervention)				
Stroke	Severe	No	Unrelated	Unexpected
Small cell lung cancer	Fatal	Yes	Unrelated	Unexpected
Constipation	Moderate	No	Unrelated	Unexpected
COVID	Severe	No	Unrelated	Unexpected
Heart failure	Moderate	No	Unrelated	Expected
Cor pulmonale	Moderate	No	Unrelated	Expected
Musculoskeletal chest pain	Moderate	No	Unrelated	Unexpected
Metastatic breast cancer	Fatal	.	Unrelated	Unexpected
Shortness of breath	Moderate	No	Unrelated	Unexpected
Drug reaction (rash)	Mild	No	Unrelated	Unexpected
SM plan and RP (best usual care)				
Heart failure	Severe	No	Unrelated	Expected
COVID	Severe	No	Unrelated	Unexpected
Heart block	Mild	Yes	Unrelated	Unexpected

TABLE 8 Serious adverse events (*continued*)

Summary of SAE	Severity	Life-threatening	Relatedness	Expectedness
Deep-vein thrombosis (DVT)	Moderate	No	Unrelated	Unexpected
Heart failure	Moderate	No	Unrelated	Expected
Heart failure	Moderate	No	Unrelated	Unexpected
COVID	Fatal	No	Unrelated	Expected

TABLE 9 Characteristics of sputum study participants

	SM plan and RP (best usual care)	Colour chart, SM plan and RP (intervention)	Total
	N = 19	*N* = 19	*N* = 38
Demographic and other baseline variables			
Age at randomisation (years)			
Mean (SD, *N*)	65.9 (10.5, 19)	66.7 (7.3, 19)	66.3 (8.9, 38)
Gender, n (%)			
Male	11 (58%)	10 (53%)	21 (55%)
Female	8 (42%)	9 (47%)	17 (45%)
Ethnicity, n (%)			
White – British/English/Northern Irish/ Scottish/Welsh	17 (89%)	19 (100%)	36 (95%)
Asian and Asian British – Indian	1 (5%)	0 (0%)	1 (3%)
Black and Black British – African Caribbean	1 (5%)	0 (0%)	1 (3%)
BMI (kg/m²)			
Mean (SD, *N*)	27.5 (6.5, 19)	27.4 (6.8, 19)	27.5 (6.6, 38)
Education level, n (%)			
No formal education	5 (26%)	5 (26%)	10 (26%)
GCSE, CSE, O level or equivalent	8 (42%)	8 (42%)	16 (42%)
A level/AS level or equivalent	2 (11%)	2 (11%)	4 (11%)
Degree level or higher	2 (11%)	4 (21%)	6 (16%)
Others (please specify)	2 (11%)	0 (0%)	2 (5%)
Medical history (baseline)			
Hospitalisations for COPD in previous year			
Median [IQR, *N*]	0.0 [0.0–0.0, 19]	0.0 [0.0–2.0, 19]	0.0 [0.0–1.0, 38]
Most recent eosinophil count			
Mean (SD, *N*)	0.2 (0.1, 14)	0.2 (0.1, 12)	0.2 (0.1, 26)
Chronic asthma, *n* (%)	5 (26%)	4 (21%)	9 (24%)
Bronchiectasis, *n* (%)	5 (26%)	7 (37%)	12 (32%)
Diabetes, *n* (%)	5 (26%)	1 (5%)	6 (16%)

continued

TABLE 9 Characteristics of sputum study participants (*continued*)

	SM plan and RP (best usual care)	Colour chart, SM plan and RP (intervention)	Total
	N = 19	*N* = 19	*N* = 38
CVA/stroke/TIA, *n* (%)	1 (5%)	1 (5%)	2 (5%)
Osteoporosis, *n* (%)	2 (11%)	6 (32%)	8 (21%)
Hypertension, *n* (%)	9 (47%)	4 (21%)	13 (34%)
Arthritis, *n* (%)	6 (32%)	6 (32%)	12 (32%)
Coronary heart disease, *n* (%)	3 (16%)	2 (11%)	5 (13%)
Depression/anxiety, *n* (%)	7 (37%)	4 (21%)	11 (29%)
GORD, *n* (%)	5 (26%)	7 (37%)	12 (32%)
Smoking status (baseline)			
Current smoking status, n (%)			
Current smoker	4 (21%)	4 (21%)	8 (21%)
Ex-smoker	13 (68%)	9 (47%)	22 (58%)
Never smoked	2 (11%)	6 (32%)	8 (21%)
Duration of smoking (years)			
Mean (SD, *N*)	35.8 (18.6, 17)	41.2 (12.5, 12)	38.0 (16.3, 29)
Medical measurement (baseline)			
FEV1: Pre bronchodilator (litres)			
Mean (SD, *N*)	1.2 (0.4, 11)	1.5 (0.7, 8)	1.3 (0.6, 19)
FEV1: Post bronchodilator (litres)			
Mean (SD, *N*)	1.6 (0.7, 11)	1.7 (0.5, 11)	1.7 (0.6, 22)
FVC: Pre bronchodilator (litres)			
Mean (SD, *N*)	2.9 (1.0, 11)	3.7 (1.5, 7)	3.2 (1.2, 18)
FVC: Post bronchodilator (litres)			
Mean (SD, *N*)	3.0 (1.0, 11)	3.1 (0.6, 10)	3.0 (0.8, 21)
MRC Breathlessness Scale, n (%)			
Grade 2	2 (11%)	5 (26%)	7 (18%)
Grade 3	6 (32%)	4 (21%)	10 (26%)
Grade 4	9 (47%)	8 (42%)	17 (45%)
Grade 5	2 (11%)	2 (11%)	4 (11%)

TABLE 10 Odds of purulent sputum sample

Variable	Odds ratio	95% CI
Exacerbation	0.98	0.28 to 1.58
Positive sample for PPB	0.78	0.19 to 3.05
Bronchiectasis	4.41	1.25 to 18.08

H. influenzae and one *Citrobacter freundii*) and one-fourth to doxycycline (*Proteus* spp.). About one-fourth (*Pseudomonas* spp.) was resistant to both amoxiclav and doxycycline. In only one case, the recovered pathogen was not susceptible to the antibiotic in the patient's RP. There was no difference in resistance between trial arms.

E-diary substudy

In total, there were 11 patients who were issued an e-diary and handed it in at the end of the trial: 6 control subjects and 5 in the intervention arm. One patient in the control group completed only 1 day of data and therefore was removed from the analysis. This number was lower than the intended recruitment target due to early termination of the study. The rate of recruitment to the e-diary substudy was proportional to the recruitment to the main study (around 10%). The demographic table of patient characteristics is summarised in *Table 11*.

The median completion percentage of the e-diary from the day of first entry to the day of last entry was 49.4% (first quartile 36.7, third quartile 70.8), with an improvement of median data completion to 71.6% after imputation (*Figure 8*). Median follow-up was 10.6 months (first quartile 4.3, third quartile 12.0). One participant withdrew from the study early due to the perceived burden of study questionnaires, and another stopped the substudy early, as he thought it had ended. In total, 42 exacerbations were identified. The median number of exacerbations during follow-up was 4 (2, 6.75). Two patients had 10 exacerbations. The annualised rate of exacerbations was 9.1 (IQR 2.8) for the control group and 5.8 (IQR 0.86) for the intervention group.

Figure 9 shows mean symptom scores during an exacerbation episode. Treated exacerbations tended to have lower baseline symptom scores and a higher rise in symptoms score compared to untreated exacerbations. For example, the day prior to a symptom defined exacerbation (Day 1) had a mean symptom score of 29.4 (± 5.7) for untreated episodes versus 20.5 (± 5.9). This may suggest that patients with a higher burden of symptoms day to day

TABLE 11 Characteristics of e-diary study participants

	Colour chart, SM plan and RP (intervention)	SM plan and RP (best usual care) Control	Total
	N = 5	*N* = 5	*N* = 10
Age (years)	68.6 (4.6, 5)	65.7 (4.0, 5)	67.1 (4.3, 10)
Male (%)	4 (80%)	3 (60%)	7 (70%)
BMI (kg/m^2)	27.8 (6.3, 5)	27.3 (8.2, 5)	27.5 (6.9, 10)
Current smoking status, n (%)			
Current smoker	0 (0%)	1 (20%)	1 (10%)
Ex-smoker	4 (80%)	4 (80%)	8 (80%)
Never smoked	1 (20%)	0 (0%)	1 (10%)
Duration of smoking (years)	43.8 (15.5, 4)	42.6 (11.5, 5)	43.1 (12.5, 9)
Cigarettes per day	25.0 (., 1)	11.7 (7.6, 3)	15.0 (9.1, 4)
COPD GOLD stage			
Category C	2 (40%)	0 (0%)	2 (20%)
Category D	3 (60%)	5 (100%)	8 (80%)
Most recent blood eosinophils	0.2 (0.1, 3)	0.2 (0.1, 5)	0.2 (0.1, 8)
FEV1: Post bronchodilator (litres)	1.8 (0.6, 1)	1.6 (0.6, 1)	1.7 (0.1, 2)
FVC: Pre bronchodilator (litres)	3.9 (0.9, 4)	2.9 (., 1)	3.7 (0.9, 5)
MRC Breathlessness Scale, n (%)			
Grade 2	3 (60%)	0 (0%)	3 (30%)
Grade 3	0 (0%)	1 (20%)	1 (10%)
Grade 4	2 (40%)	4 (80%)	6 (60%)

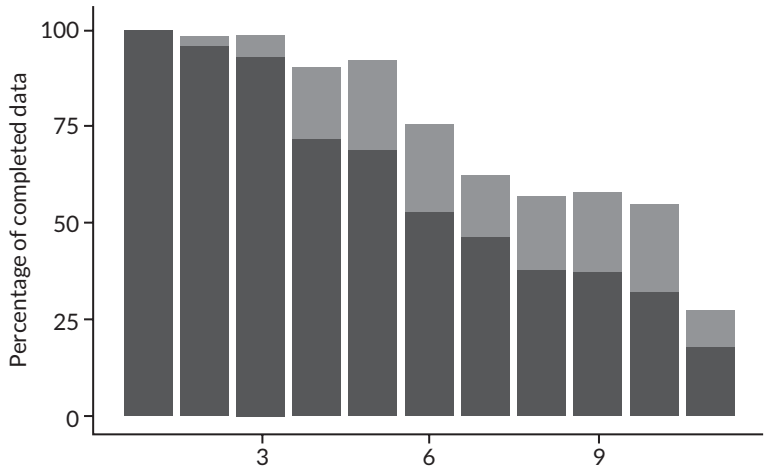

FIGURE 8 Percentage completion of data before and after imputation.

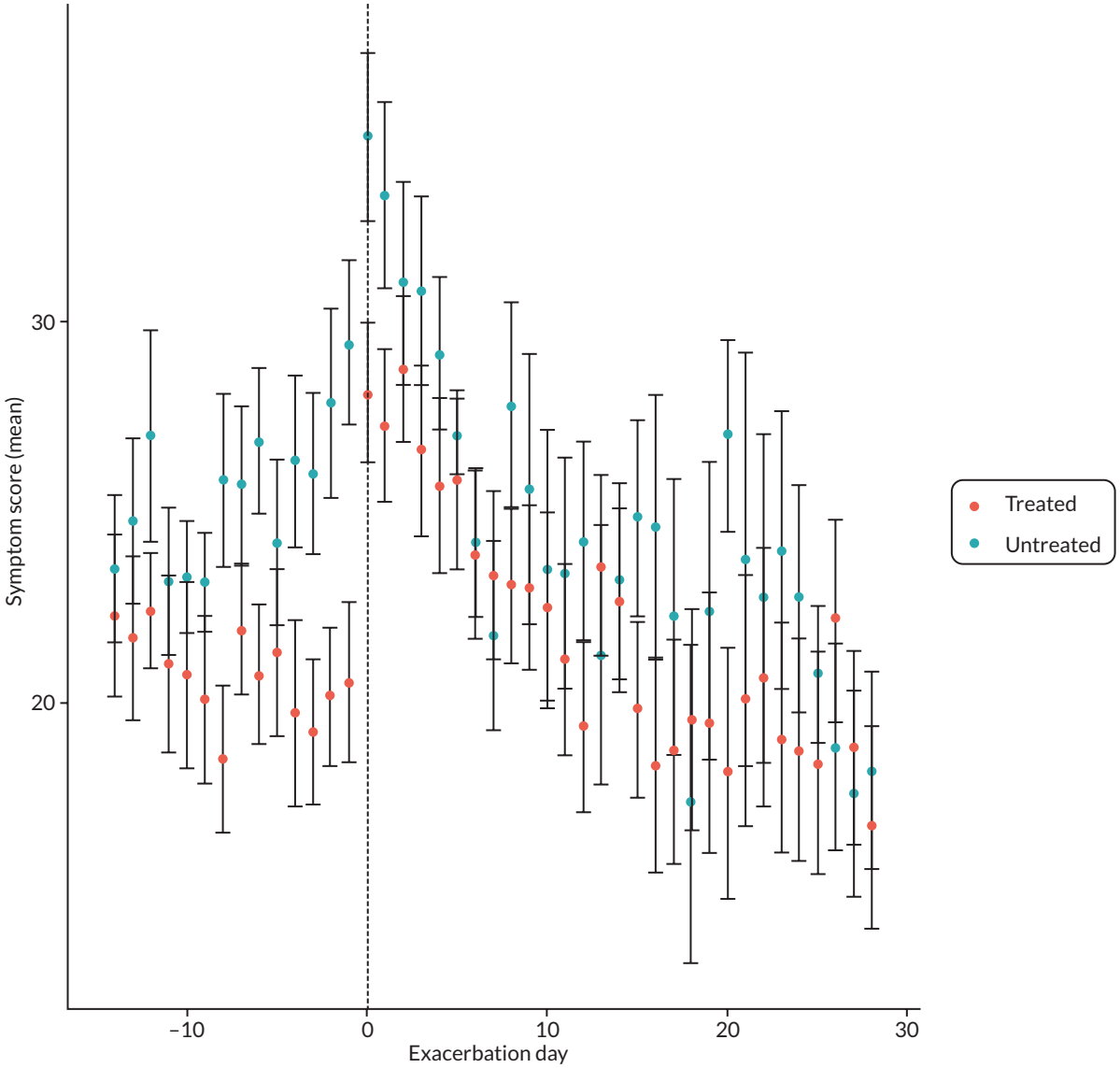

FIGURE 9 Mean symptom diary score across the time course of an exacerbation. Note: Day 0 = onset of exacerbation. Error bars represent standard error of the mean.

may experience symptom-defined exacerbations but fail to recognise their significance. There was also a higher symptom peak for treated exacerbations with a difference of 7.6 compared to 5.5 in untreated episodes, which likely informed the decision to treat. There was a trend towards a slower recovery in patients with untreated exacerbations. For the results in *Figure 9*, there were no statistically significant differences due to low patient numbers, though the trend aligns with data from a previous study of exacerbations in alpha 1 antitrypsin deficiency-related lung disease.[54] *Figure 10* shows exacerbations on an individual patient level.

Qualitative substudy

Results of the acceptability parts of the substudy are reported in the threaded publication.[51]

There were two aspects of our work not reported in this paper, namely process evaluation regarding declining participation, and the impact of MLTCs. No one accepted our invitation to participate in the decliners' questionnaire. However, we explored this question when interviewing HCPs who had been involved in recruiting for the trial. Healthcare professionals often said that they had missed the opportunity, or forgotten, to invite decliners to complete the decliners' questionnaire. One HCP commented that for other studies, they rarely got slips returned declining participation, but that examples had included caring responsibilities. Six participants had caring responsibilities themselves. A number of participants described a symbiotic relationship, where each person was capable of different things, and between them, they were able to work together.

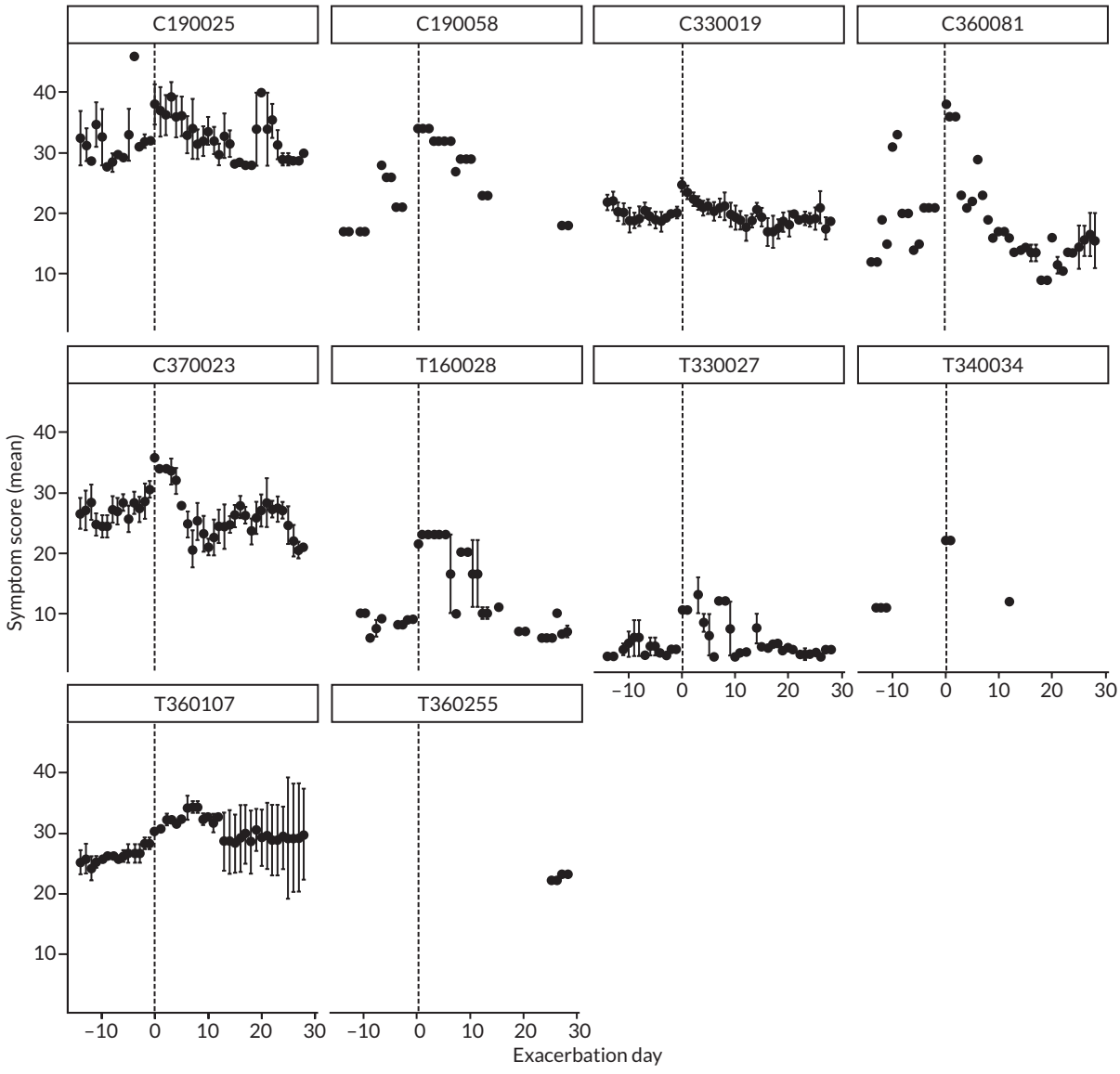

FIGURE 10 Individual mean symptom score data across exacerbations. Note: Error bars represent standard error of the mean.

> *He goes to the shop, I do his medication, I generally cook the meals … But we just do what we can for each other.*
>
> *P1*

Additional reasons as to why patients did not want to participate included patients feeling overwhelmed either by the amount of paperwork they received in the invitation exacerbated by the additional substudies, their already complex lives (e.g. family or financial difficulties and caring responsibilities for grandchildren), a lack of interest in using RPs, misunderstandings such as undesired limitations being made on their usage of their RP, and ward patients who on discharge still felt too unwell to participate. A number of the HCPs were disappointed that the trial had closed early and were keen to register their interest if it were to recommence at any stage. An enabler identified by one HCP was the amount of attention patients get while participating in a trial, which was a driver to enrol for some.

Multiple long-term conditions

Forty-three interviews were conducted with 39 patients. Patient characteristics are reported in the qualitative substudy's main paper. Overall, we did not identify any areas where those with MLTCs experienced SM differently from other patients. We report our analysis here under four different areas:

- experience of managing MLTCs
- treatment burden
- symptom interpretation
- MLTCs as a barrier to exercise.

Experience of managing MLTCs

When interviewing participants, we targeted those with MLTCs recorded at baseline. However, for most patients, these comorbidities simply amounted to having to take additional medication each day. For a couple of patients, the fact that they took so much medication each day was a reason to be hesitant about using their RPs. Although some participants expressed feelings of fear and anxiety, what was most notable was their stoical acceptance and resignation towards their health.

> *[Managing MLTCs] it's the same as Winston Churchill quote isn't it? "Keep buggering on."*
>
> *P27*

Treatment burden

Due to the limitations of our sample characteristics (i.e. that their MLTCs were generally well controlled), very few of our participants reported treatment burden. P35 explained that during an exacerbation, they had to take 30 tablets a day, in addition to inhalers and insulin. The chemist had been unable to provide a blister pack to help.

> *It would really help me to get a blister pack for my medication, that would really help. But since I've had my chemist, the local chemist [inaudible]. But I'm dealing with it at the moment.*
>
> *P35*

On the whole, participants did not mind attending appointments. Things that did concern them were attending for appointments that turned out to be a 'waste' (P31) of time.

> *I said, what's the point? I'm going parking up, trying to park in an hospital takes ages to get into to be told, "We're doing nothing, go away, live with it".*
>
> *P16*

Issues around the logistics of getting to an appointment were well described by P22's various experiences as an oxygen user who had also lost the use of their dominant hand due to nerve damage and was on diuretics. A 9 a.m. appointment would have meant getting up at 3 a.m. in order to negotiate all of these factors. Prior to being issued with ambulatory oxygen, they were out of the house for 4 hours when utilising patient transport with oxygen just for a 5-minute chest X-ray. Attending early appointments with a carer once ambulatory oxygen was supplied was equally challenging:

> *But of course once as I got worse I would have to be with [them], so I wasn't dropped off [at the front entrance] anymore. So you have to get there early, and you have to be more organised. It's that kind of thing, and then of course trying to park at the [hospital], especially in the morning is nigh on impossible, it's absolutely horrific.*
>
> *P22*

Symptom interpretation

When targeting participants, we prioritised those with comorbidities that might also induce cough, for example, coronary heart disease and gastro-oesophageal reflux disease. However, on the whole, participants did not recognise that there could be difficulties around differentiating their COPD cough from cough due to other causes.

Multiple long-term conditions as a barrier to exercise

The key theme identified in relation to MLTCs within our data was MLTCs as a barrier to exercise. This primarily related to conditions which caused pain, for example, arthritis and the limitations that this imposed on not only exercise but also activity generally.

> *If my knees was all alright my breathing would be better, I know that for definite. Because you can tell by the distance you walk that I could try to walk from here to [hospital] today if my knees was alright, because I would be able to breath and walk and take my time and carry on, you know what I mean? If the knee is not right and your whole body is not right then you're not going to do it are you?*
>
> *P12*

For a number of patients, their comorbidities had a bigger impact on their lives than their COPD.

> *I've been hospitalised with the gallbladder 4 times in the last year, 2 years, and it nearly killed me 2 years ago, and [my COPD's] too bad for them to operate, so stuck with it for life now, until the point where it kills me, because it's going rupture again one day. … But there you go.*
>
> *P11*

Discussion

Overall, the results do not support routine use of colour charts as an adjunct to SM, but great caution must be exercised in interpretation, since the study under-recruited. While QoL was better in colour chart users at 12 months, this could be a spurious result and is not offset by the potential adverse impact on hospitalisations and treatment failure after initial AECOPD management. It remains possible that the adverse effects seen were a chance finding, or resulted from imbalances in the rate of NIV and oxygen use, or in the rate of bronchiectasis between arms.

Utility of colour chart

Although the study under-recruited significantly, the trends seen in the data towards more hospitalisations in the intervention arm and more second courses of treatment required for AECOPD imply that further study of a colour chart as a means of choosing to use the antibiotic component of a RP may be inappropriate. If this trend had continued through to the numbers planned for the pilot (*n* = 495), it might have been a significant safety issue. The pattern of increased hospitalisations, mainly for AECOPD, but possibly also higher for other reasons as shown in the SAEs (see *Table 8*), could have been influenced by small differences in baseline characteristics in the groups not captured by use of GOLD severity grading for COPD. Specifically, LTOT and home NIV use was more prevalent in colour chart users; both these factors are indicative of very severe disease and have been shown to relate to higher admission rates previously.[14,55,56] Cor pulmonale also occurred in this group as a SAE, consistent with very severe disease. Unmeasured severity factors such as comorbid bronchiectasis not diagnosed as yet could have occurred as well.

The results for QoL were somewhat counterintuitive; they felt better despite being admitted to hospital more and experiencing more requirement for additional treatment. Patients were well matched at baseline for QoL scores, and our analysis accounted for baseline score and other potential influences on QoL such as disease severity. If anything, since very severe disease not captured by GOLD stage was more common in the colour chart group, we would have expected them to feel worse, but this was not the case. It is possible that the large number of admissions, and recurrent admissions, led to greater use of community respiratory services or additional support being put in place for patients that was not captured by our medication histories and simple healthcare utilisation measures, and which aided QoL. The more detailed economic analysis which was abandoned due to early study cessation might have picked this up. Alternatively, the colour chart might have improved patient confidence in recognition of symptoms, and improved QoL as a result. The e-diary was unable to comment on whether confidence in SM, or better SM, occurred in patients who had a chart due to the low numbers enrolled. Taken at face value, higher rates of hospitalisation and more antibiotic courses imply ineffective SM, which is why we feel this is a less likely explanation.

Bronkotest was selected as the intervention to guide SM of antibiotic usage, based on the assumption that presence of a bacterium will result in increased neutrophil (and myeloperoxidase) burden, detectable by colour, as explained in the introduction, based on past literature. However, our findings in the sputum substudy showed that presence of a PPB was not independently associated with purulent sputum, and that coexistence of bronchiectasis was associated with a fourfold increase in risk of purulent sputum, independent of disease state and

presence of a PPB. Bronchiectasis, a common comorbidity in COPD present in 22% of our participants, is associated with a significant neutrophilic burden,[57] and our findings may suggest that the Bronkotest is less specific in this cohort of patients. We had deliberately kept our inclusion criteria broad, because comorbidity (both respiratory and otherwise) is common in COPD, and we wanted to test if the intervention was useful in all COPD patients, as opposed to specific subgroups. We did not directly review CT scan images or reports to confirm bronchiectasis, and it is possible that undiagnosed bronchiectasis was present in some of the COPD patients enrolled. We needed to be pragmatic about the number of minimisation variables we included, and chose to include chronic bronchitis instead of bronchiectasis, reasoning that clinically significant bronchiectasis would usually lead to regular sputum production, and data on this symptom might be more readily available than a CT scan in a primary care setting. However, the findings here, and in other work, about sputum colour and bacterial load in bronchiectasis specifically, might make bronchiectasis a better choice for minimisation in any future similar work.

The sputum data suggested that utility of a sputum colour chart could be impaired unless selecting patients carefully for absence of bronchiectasis. Consistent with this, a recent systematic review has shown only moderate specificity and poor sensitivity of colour for bacterial presence.[57] Indeed, multiple studies have shown this, albeit not all before our trial began. A study from the Netherlands reported a very weak association between bacterial load and sputum colour, with no difference in bacterial load between patients with purulent sputum or not. Also, there was no consistent relationship between change in sputum colour and change in bacterial load during admission.[57] In another study, the mucus score, not necessarily purulence, was the earliest determinant of exacerbation.[59] Furthermore, in patients with asthma, eosinophilic sputum may also be purulent.[60] This body of evidence brings into question whether routine adoption of colour alone, as opposed to a broader picture of symptoms and other features, personalised to the patient, is appropriate within either another trial or routine care.

Level of bacterial colonisation when stable, and infection at exacerbation, was like that observed in larger COPD cohorts:[62,63] approximately, a quarter of stable state samples and half of exacerbation samples. The choice of RP antibiotics was generally appropriate based on bacteria present.

Managing chronic obstructive pulmonary disease trials in primary care

We experienced a range of interactions across the primary care research landscape. Our lead CRN designed searches aimed at facilitating pre-screening in primary care, which was helpful, but slowed us down somewhat because other CRNs were ready prior to them. In general, the national CRN network was very helpful in identifying regions and sites wanting to participate. It became apparent early in the study that aligning study visits to usual care did not happen – we had deliberately made our protocol visits and data collection match closely to the frequency of visit and data required at annual review within primary care for COPD [part of the Quality and Outcomes Framework (QOF)], so that sites could operationalise the study by consenting and collecting data at annual COPD review in year 0, and follow-up review at the end of 1 year. However, sites informed us that the teams doing research are different from those seeing for chronic care reviews, hence the appointments usually ended up being duplicated. This suggests that wider training or delegation of duties (from clinical to research staff or vice versa) might help, and that the costing template which offsets budget for study procedures that are typically part of routine care may not work well in all cases.

Some ideas emerged from running the study, either suggested by sites or patients, or tried in some of our sites. These included routine use of reply slips and freepost envelopes to express interest after the pre-screening invite was sent by the practice. This was deemed better than text or online response, even though the latter is the more usual way that studies are moving, to reduce paper waste and improve speed. Financing research nurses that can offer home visits was suggested; while such teams do exist in some areas, there is an additional cost, and it is unlikely this would be feasible in NIHR studies. Commercial trials offer this much more routinely now, which may make lower-budget NIHR studies less attractive to patients by comparison. Research clinics dedicated to seeing all trial patients were used in some larger practices, but many had their dedicated nurses and rooms removed during the pandemic; national surveys to ascertain the degree to which these have returned may help assessment of feasibility. A5 glossy booklet rather than locally printed A4 sheets were felt to be more attractive for study materials but can be difficult to produce locally, take space to store (which is often lacking in practices) and are more expensive to produce irrespective of where that is done.

Barriers to studies of self-management

These were largely the same as in routine medical care, but perhaps indicated some biases on the part of practitioners with multiple assumptions made about how patients wanted to be treated and the degree to which they wanted to participate in their own care. The fidelity data showed that good-quality SM was being delivered, at least in terms of measurable tasks (see *Figure 6*), but the dissonance with qualitative data was concerning. Fidelity data were collected at 2 weeks, and qualitative data were collected at a range of time points, which may suggest information is poorly retained, or that factual data were less important than a later internal perception of self-efficacy. We had planned to collect data on self-efficacy via the PROMIS questionnaire, as part of our MLTC add-on, but this was not possible when funding was stopped; this could have been helpful in interpreting the data, had we recruited to target. With the small numbers we did have, it is unlikely it would have impacted interpretation of this specific study. Proper observation of consultations would have been helpful through the planned video-recording, and might be considered as part of any future work into fidelity of SM in routine care.

Impact of MLTCs

Overall, we did not identify any areas where those with MLTCs experienced SM differently from other patients and suggest that patients with MLTCs did not have any additional difficulties with symptom interpretation or SM of AECOPD compared with other participants in the trial. Low numbers meant that exploratory quantitative analysis of the impact of the intervention split by presence of MLTCs would not have been meaningful, hence was not completed. We were able to demonstrate through qualitative work that patients had not given MLTCs as a reason for not participating in the trial and were able to demonstrate that patients with caring responsibilities, who had a symbiotic relationship with the persons they cared for/received care from, had participated. However, the patients we spoke to with MLTCs affecting major organs were not burdened by them; on the whole, these were well managed with medication. Notably, such participants took a stoical approach to their health. Treatment burden was largely centred around the number of medications the participants had to take and appointments that turned out to be a 'waste' of time, and logistics of getting to appointments with limited parking spaces allocated to disabled users particularly, and early-morning appointments, the preparation for which was inhibited by medications (e.g. diuretics), and the amount of time required to actually get ready in the mornings. Patients had not identified difficulties with differentiating the underlying causes of cough. Importantly, the key area where MLTCs impacted was that of exercise, which is an important factor in staying healthy, thereby reducing the likelihood and impact of exacerbations in COPD.

What we see here very much relates to work relating to that of Bury's biographical disruption,[63] that is, that these participants are already managing, and dealing with the impact of health issues as well as other things in their lives, and that issues relating to research and SM of AECOPD are just additional things to be factored in. Rather than resulting in any evidence in their narratives of having reached a breaking point, these additional factors merely deepen the challenges that they are already experiencing. What we cannot identify from these findings is what the tipping point is, or, in Bury's terms, what 'disruptive' event might tip their experience over into being something fundamentally different.

Strengths and limitations

A strength is that we were able to complete all aspects of assessment of acceptability, and most of the process evaluation. The sputum substudy data and limited effectiveness analyses are sufficient to deprioritise further studies of colour charts, at least in an unselected COPD population. We were unable to get any patients to complete our decliner survey to understand why they chose not to participate, which limited our process evaluation a little; this will have been driven partly by early cessation and fewer active sites or approaches to patients being made. However, there were lessons learnt about trial processes and overlaps between qualitative and quantitative study processes (reported above) which also contributed. Most of our limitations relate to the early trial cessation, which resulted in less health economic data collection, no economic analysis, smaller trial fidelity analyses, no self-efficacy data collection and severe under-recruitment.

Future research

Given that the trial under-recruited and we cannot be certain of the results, repetition in a higher risk population in secondary care, with more careful exclusion of bronchiectasis, might be considered, although this has risks of poor generalisability to routine practice. Development of very brief, 30-second advice, that can be used for antimicrobial stewardship (AMS) in consultations with patients, modelled on that of the 'Very Brief Advice' used for smoking cessation in consultations[64] may be more useful than specifically adding a colour chart, at least on the strength of our fidelity data and qualitative work. Attitudes to antibiotics and whether or not the trial had impacted on these were not explored because the trial did not explicitly set out to change them, but the qualitative team felt this was an emergent area and have since conducted other work

exploring this, which is in preparation. In addition, further research is needed on how patients across the board make sense of different sources of knowledge related to AMS, including those without experience of particular common conditions predisposing to infection. Linguistic analyses of the language used by patients and HCPs in relation to exacerbations, and literature relating to the management of AMS and AECOPD, may also be interesting. To better understand the impact of MLTCs, a focused study, with a sensitive, flexible and perhaps creative design, for example, along the lines of purposively sampled case studies and/or ethnographic research, may reveal a more complex and nuanced picture than we were able to. Analysis of cohort data, perhaps from real-world sources, looking at the efficacy of COPD treatment stratified by the presence of MLTCs could also be considered.

Conclusion

Due to under-recruitment, we cannot be certain of our results; however, it seems unlikely that the Bronkotest colour chart is appropriate for routine use in COPD care.

Patient and public involvement

Patient and public involvement (PPI) was integral to the project from commencement. A specific PPI group (n = 8) was convened by the study team in Salford to advise on patient facing study materials, and the initial face-to-face meeting in late 2019 was cochaired by a patient co-applicant (KW) and Dr Bakerly (NB). The PPI group reviewed the trial-specific materials and approved the topic guide and patient information sheet (PIS), after some minor changes were made. Fortunately, we were able to produce our video PIS with a patient prior to the first COVID lockdown, and we also co-designed materials to aid patients in sputum sample processing and submission, specifically a leaflet and some video resources, the latter of which were used mainly in staff training in the end. One hundred and twenty patients engaged with this exercise via surveys, as did 50 HCPs, and 10 patients met with us remotely to discuss co-design in more detail. We worked with our other patient co-applicant (IB) and the Birmingham University respiratory patient advisory group (PAG) to recruit four patient co-researchers for the qualitative work planned from mid-2020 onwards, although a University COVID recruitment freeze delayed formalising this for several months. Patient and public involvement engagement was completed virtually in mid- to late 2020 to discuss and design adaptations to the protocol to make it acceptable to patients and feasible during the various COVID lockdowns. In 2021, six of the PAG group downloaded the e-diary and refined its design to make it more patient-friendly. As a result of this feedback, changes were made to the question descriptions and language used (e.g. informing participants that sputum is sometimes referred to as 'mucus' or 'phlegm'). Feedback from the PAG testing also helped inform the study's 'Frequently Asked Questions' section and the instructions about downloading the app. Study updates occurred regularly via our PAG newsletters and meetings through to the time of the reset process, at which point we met with them to discuss proposed changes to the study, and ultimately the decision to close. After the decision to close, the qualitative team worked closely with our patients to train them in qualitative data analysis and coproduce the analysis of the acceptability data;[51] two patients contributed substantially and were authors on the academic paper. At the end of the study, we produced a written lay summary with the PAG for circulation in the newsletter and discussed its findings in a meeting.

In addition, we had a patient on our Trial Steering Committee (TSC) and invited a patient co-applicant to the Trial Management Group (TMG) (IB); he was unable to attend many meetings due to illness and died during the study.

Equality, diversity and inclusion

While every attempt was made to include diverse participants, this was not achieved with regard to race. We were able to recruit diverse participants with regard to educational level, perhaps reflecting many sites (especially the two secondary care sites) being located in areas of high social deprivation. However, a lack of diversity is not necessarily due to systemic biases in recruitment, and could have been contributed to by early termination.

Additional information

CRediT contribution statement

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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.

Ethics statement

Colour-COPD studies were reviewed by the Yorkshire and the Humber – South Yorkshire REC (20/YH/0273) and all participants gave informed consent. Ethical approval was granted on 4 November 2020.

Information governance statement

The University of Birmingham is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, University of Birmingham is the Data Controller, and you can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for our Data Protection Officer.

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/KPFD5558.

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Department of Health and Social Care disclaimer

Publications

Channa S, Gale N, Lai E, Hall L, Quinn M, Turner AM. Colour vision deficiency and sputum colour charts in COPD patients: an exploratory mixed-method study. *npj Prim. Care Respir Med* 2021:**31**;13. https://doi.org/10.1038/s41533-021-00225-z

Adams RL, McKenna M, Allsopp K, Saleem S, Le Mesurier N, Diar Bakerly N, *et al*. "I know this is on my chest, let's act": a qualitative study exploring self-management of acute COPD exacerbations with a sputum colour chart to reduce unnecessary antibiotic use. *npj Prim Care Respir Med* 2024;**34**:41. https://doi.org/10.1038/s41533-024-00398-3

Trial registration

This trial is registered as ISRCTN14955629.

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This synopsis provided an overview of the research award Sputum colour charts to guide antibiotic self-treatment of acute exacerbation of COPD (Colour-COPD). For more information about this research, please view the award page (https://fundingawards.nihr.ac.uk/award/17/128/04).

About this synopsis

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List of abbreviations

aRD	adjusted risk difference
aRR	adjusted relative risk
AECOPD	acute exacerbation of chronic obstructive pulmonary disease
AMS	antimicrobial stewardship
BCTU	Birmingham Clinical Trials Unit
BMI	body mass index
CAT	COPD assessment test
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease

CPRD	Clinical Practice Research Datalink
CRF	case report form
CRN	Clinical Research Network
DTT	dithiothreitol
DVT	deep-vein thrombosis
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
EXACT	EXAcerbations of Chronic Pulmonary Disease Tool
FEV1	forced expiratory volume in 1 second
FVC	forced vital capacity
GLI	Global Lung Function Initiative
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	general practitioner
HCP	healthcare professional
HRA	Health Research Authority
HRQoL	health-related quality of life
HRU	health resource usage
ICS	inhaled corticosteroid
IQR	interquartile range
IRR	incidence rate ratio
ITT	intention to treat
LABA	long-acting beta 2 agonist
LAMA	long-acting muscarinic antagonist
LR	likelihood ratio
LTOT	long-term oxygen therapy
MLTC	multiple long-term conditions
MRC	Medical Research Council
NIHR	National Institute for Health and Care Research
NIV	non-invasive ventilation
PAG	patient advisory group
PIS	patient information sheet
PPB	potentially pathogenic bacterium
PPI	patient and public involvement
PROMIS	Patient-Reported Outcomes Measurement Information System
QOF	Quality and Outcomes Framework
RD	risk difference
SAE	serious adverse event
SM	self-management
TMG	Trial Management Group
TSC	Trial Steering Committee

References

1. *The Battle for Breath – The Impact of Lung Disease in the UK*. British Lung Foundation; 2016. URL: www.asthmaandlung.org.uk/battle-breath-report
2. Bowerman C, Bhakta NR, Brazzale D, Cooper BR, Cooper J, Gochicoa-Rangel L, *et al*. A race-neutral approach to the interpretation of lung function measurements. *Am J Respir Crit Care Med* 2023;**207**:768–74.
3. Diao JA, He Y, Khazanchi R, Nguemeni Tiako MJ, Witonsky JI, Pierson E, *et al*. Implications of race adjustment in lung-function equations. *N Engl J Med* 2024;**390**:2083–97.
4. *Global Initiative for Obstructive Lung Disease*. URL: www.goldcopd.com (accessed 1 October 2024).
5. 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.
6. Lopez-Campos JL, Marquez-Martin E, Soriano JB. The role of air pollution in COPD and implications for therapy. *Expert Rev Respir Med* 2016;**10**:849–59.
7. Sethi S, Sethi R, Eschberger K, Lobbins P, Cai X, Grant BJ, Murphy TF. Airway bacterial concentrations and exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007;**176**:356–61.
8. Miravitlles M, Kruesmann F, Haverstock D, Perroncel R, Choudhri SH, Arvis P. Sputum colour and bacteria in chronic bronchitis exacerbations: a pooled analysis. *Eur Respir J* 2012;**39**:1354–60.
9. Ritchie AI, Wedzicha JA. Definition, causes, pathogenesis, and consequences of chronic obstructive pulmonary disease exacerbations. *Clin Chest Med* 2020;**41**:421–38.
10. Vijayasaratha K, Stockley RA. Reported and unreported exacerbations of COPD: analysis by diary cards. *Chest* 2008;**133**:34–41.
11. Leidy NK, Murray LT, Jones P, Sethi S. Performance of the EXAcerbations of chronic pulmonary disease tool patient-reported outcome measure in three clinical

trials of chronic obstructive pulmonary disease. *Ann Am Thorac Soc* 2014;**11**:316–25.

12. Langsetmo L, Platt RW, Ernst P, Bourbeau J. Underreporting exacerbation of chronic obstructive pulmonary disease in a longitudinal cohort. *Am J Respir Crit Care Med* 2008;**177**:396–401.
13. Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002;**57**:847–52.
14. Bahadori K, FitzGerald JM, Levy RD, Fera T, Swiston J. Risk factors and outcomes associated with chronic obstructive pulmonary disease exacerbations requiring hospitalization. *Can Respir J* 2009;**16**:e43–9.
15. Roberts CM, Stone RA, Lowe D, Pursey NA, Buckingham RJ. Co-morbidities and 90-day outcomes in hospitalized COPD exacerbations. *COPD* 2011;**8**:354–61.
16. Beasley V, Joshi PV, Singanayagam A, Molyneaux PL, Johnston SL, Mallia P. Lung microbiology and exacerbations in COPD. *Int J Chron Obstruct Pulmon Dis* 2012;**7**:555–69.
17. *Chronic Obstructive Pulmonary Disease: NICE Guideline*; 2010. URL: www.nice.org.uk/guidance/ng115
18. Majothi S, Jolly K, Heneghan NR, Price MJ, Riley RD, Turner AM, *et al*. Supported self-management for patients with COPD who have recently been discharged from hospital: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis* 2015;**10**:853–67.
19. Jolly K, Majothi S, Sitch AJ, Heneghan NR, Riley RD, Moore DJ, *et al*. Self-management of health care behaviors for COPD: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis* 2016;**11**: 305–26.
20. Lenferink A, Brusse-Keizer M, van der Valk PD, Frith PA, Zwerink M, Monninkhof EM, *et al*. Self-management interventions including action plans for exacerbations versus usual care in patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2017;**8**:CD011682.
21. Blackmore C, Johnson-Warrington VL, Williams JE, Apps LD, Young HM, Bourne C, Singh SJ. Development of a training program to support health care professionals to deliver the SPACE for COPD self-management program. *Int J Chron Obstruct Pulmon Dis* 2017;**12**:1669–81.
22. Divo M, Cote C, de Torres JP, Casanova C, Marin JM, Pinto-Plata V, *et al*.; BODE Collaborative Group. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012;**186**:155–61.
23. Sundh J, Stallberg B, Lisspers K, Montgomery SM, Janson C. Co-morbidity, body mass index and quality of life in COPD using the Clinical COPD questionnaire. *COPD* 2011;**8**:173–81.
24. Tan SL, Wood AM. Chronic obstructive pulmonary disease and co-morbidities: a review and consideration of pathophysiology. *Panminerva Med* 2009;**51**:81–93.
25. Murthy SC, Nowicki ER, Mason DP, Budev MM, Nunez AI, Thuita L, *et al*. Pretransplant gastroesophageal reflux compromises early outcomes after lung transplantation. *J Thorac Cardiovasc Surg* 2011;**142**:47–52. e3.
26. Turner AM, Tamasi L, Schleich F, Hoxha M, Horvath I, Louis R, Barnes N. Clinically relevant subgroups in COPD and asthma. *Eur Respir Rev* 2015;**24**:283–98.
27. de Torres JP, Casanova C, Marin JM, Pinto-Plata V, Divo M, Zulueta JJ, *et al*. Prognostic evaluation of COPD patients: GOLD 2011 versus BODE and the COPD comorbidity index COTE. *Thorax* 2014;**69**:799–804.
28. Hurst JR, Vestbo J, Anzueto A, Locantore N, Mullerova H, Tal-Singer R, *et al*.; Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med* 2010;**363**:1128–38.
29. Merinopoulou E, Raluy-Callado M, Ramagopalan S, MacLachlan S, Khalid JM. COPD exacerbations by disease severity in England. *Int J Chron Obstruct Pulmon Dis* 2016;**11**:697–709.
30. Iheanacho I, Zhang S, King D, Rizzo M, Ismaila AS. Economic burden of chronic obstructive pulmonary disease (COPD): a systematic literature review. *Int J Chron Obstruct Pulmon Dis* 2020;**15**:439–60.
31. Steer J, Norman EM, Afolabi OA, Gibson GJ, Bourke SC. Dyspnoea severity and pneumonia as predictors of in-hospital mortality and early readmission in acute exacerbations of COPD. *Thorax* 2012;**67**:117–21.
32. Albert RK, Connett J, Bailey WC, Casaburi R, Cooper JA Jr, Criner GJ, *et al*.; COPD Clinical Research Network. Azithromycin for prevention of exacerbations of COPD. *N Engl J Med* 2011;**365**:689–98.
33. Rodrigo-Troyano A, Suarez-Cuartin G, Peiró M, Barril S, Castillo D, Sanchez-Reus F, *et al*. *Pseudomonas aeruginosa* resistance patterns and clinical outcomes in hospitalized exacerbations of COPD. *Respirology* 2016;**21**:1235–42.
34. Stockley RA, O'Brien C, Pye A, Hill SL. Relationship of sputum color to nature and outpatient

management of acute exacerbations of COPD. *Chest* 2000;**117**:1638–45.

35. Foreman MG, DeMeo DL, Hersh CP, Reilly JJ, Silverman EK. Clinical determinants of exacerbations in severe, early-onset COPD. *Eur Respir J* 2007;**30**:1124–30.
36. Yeom HE, Lee J. The association of education level with autonomy support, self-efficacy and health behaviour in patients with cardiovascular risk factors. *J Clin Nurs* 2022;**31**:1547–56.
37. Bellg AJ, Borrelli B, Resnick B, Hecht J, Minicucci DS, Ory M, *et al*.; Treatment Fidelity Workgroup of the NIH Behavior Change Consortium. Enhancing treatment fidelity in health behavior change studies: best practices and recommendations from the NIH behavior change consortium. *Health Psychol* 2004;**23**:443–51.
38. Patel K, Smith DJ, Huntley CC, Channa SD, Pye A, Dickens AP, *et al*. Exploring the causes of COPD misdiagnosis in primary care: a mixed methods study. *PLOS ONE* 2024;**19**:e0298432.
39. Woodcock A, Boucot I, Leather DA, Crawford J, Collier S, Bakerly ND, *et al*. Effectiveness. *Eur Respir J* 2018;**51**:1701531.
40. O'Brien C, Guest PJ, Hill SL, Stockley RA. Physiological and radiological characterisation of patients diagnosed with chronic obstructive pulmonary disease in primary care. *Thorax* 2000;**55**:635–42.
41. Woolhouse IS, Hill SL, Stockley RA. Symptom resolution assessed using a patient directed diary card during treatment of acute exacerbations of chronic bronchitis. *Thorax* 2001;**56**:947–53.
42. Allegra L, Blasi F, Diano P, Cosentini R, Tarsia P, Confalonieri M, *et al*. Sputum color as a marker of acute bacterial exacerbations of chronic obstructive pulmonary disease. *Respir Med* 2005;**99**:742–7.
43. *Cleveland Color of Snot Chart*; 2017. URL: https://health.clevelandclinic.org/2014/11/whatthe-color-of-your-snot-really-means/ (accessed 1 October 2024).
44. Stolbrink M, Amiry J, Blakey JD. Does antibiotic treatment duration affect the outcomes of exacerbations of asthma and COPD? A systematic review. *Chron Respir Dis* 2018;**15**:225–40.
45. van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, *et al*. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health* 2012;**15**:708–15.
46. Rehal S, Morris TP, Fielding K, Carpenter JR, Phillips PP. Non-inferiority trials: are they inferior? A systematic review of reporting in major medical journals. *BMJ Open* 2016;**6**:e012594.
47. Machin D. *Sample Size Tables for Clinical Trials*. London: Wiley-Blackwell; 2009.
48. Roberts CM, Stone RA, Buckingham RJ, Pursey NA, Lowe D; National Chronic Obstructive Pulmonary Disease Resources and Outcomes Project implementation group. Acidosis, non-invasive ventilation and mortality in hospitalised COPD exacerbations. *Thorax* 2011;**66**:43–8.
49. Jose NC, Langel K. ePRO vs paper. *Appl Clin Trials* 2010;**19**:1–5.
50. Mackay AJ, Donaldson GC, Patel AR, Singh R, Kowlessar B, Wedzicha JA. Detection and severity grading of COPD exacerbations using the exacerbations of chronic pulmonary disease tool (EXACT). *Eur Respir J* 2014;**43**:735–44.
51. Adams RL, McKenna M, Allsopp K, Saleem S, Le Mesurier N, Diar Bakerly N, *et al*. "I know this is on my chest, let's act": a qualitative study exploring self-management of acute COPD exacerbations with a sputum colour chart to reduce unnecessary antibiotic use. *npj Prim Care Respir Med* 2024;**34**:41. https://doi.org/10.1038/s41533-024-00398-3
52. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. *BMC Med Res Methodol* 2013;**13**:117.
53. Andreen N, Westin J, Vanfleteren LEGW. Hospital admission rates in patients with COPD throughout the COVID-19 pandemic. *Int J Chron Obstruct Pulmon Dis* 2023;**18**:1763–72.
54. Ellis P, Parekh G, Duvoix A, Watson L, Sharp A, Mobeen F, *et al*. Characteristics of alpha-1 antitrypsin deficiency related lung disease exacerbations using a daily symptom diary and urinary biomarkers. *PLOS ONE* 2024;**19**:e0297125.
55. Turner AM, Sen S, Steeley C, Khan Y, Sweeney P, Richards Y, Mukherjee R. Evaluation of oxygen prescription in relation to hospital admission rate in patients with chronic obstructive pulmonary disease. *BMC Pulm Med* 2014;**14**:127.
56. Elshafei AA, Nehrenz G, Hardigan PC, Becker EA. Prediction of hospital readmission using the CORE and CORE+ scores in persons with COPD. *Respir Care* 2024:respcare.11766. https://doi.org/10.4187/respcare.11766
57. Keir HR, Shoemark A, Dicker AJ, Perea L, Pollock J, Giam YH, *et al*. Neutrophil extracellular traps, disease severity, and antibiotic response in bronchiectasis: an international, observational, multicohort study. *Lancet Respir Med* 2021;**9**:873–84.

58. Spies R, Potter M, Hollamby R, van der Walt S, Hohlfeld A, Ochodo E, Van Zyl-Smit R. Sputum color as a marker for bacteria in acute exacerbations of chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Ann Am Thorac Soc* 2023;**20**:738–48.

59. Jacobson PK, Lind L, Persson HL. The exacerbation of chronic obstructive pulmonary disease: which symptom is most important to monitor? *Int J Chron Obstruct Pulmon Dis* 2023;**18**:1533–41.

60. Simons FE. Allergic rhinobronchitis: the asthma-allergic rhinitis link. *J Allergy Clin Immunol* 1999;**104**: 534–40.

61. Armitage MN, Spittle DA, Turner AM. A Systematic review and meta-analysis of the prevalence and impact of pulmonary bacterial colonisation in stable state chronic obstructive pulmonary disease (COPD). *Biomedicines* 2021;**10**:81.

62. Bouquet J, Tabor DE, Silver JS, Nair V, Tovchigrechko A, Griffin MP, *et al*. Microbial burden and viral exacerbations in a longitudinal multicenter COPD cohort. *Respir Res* 2020;**21**:77.

63. Bury M. Chronic illness as biographical disruption. *Sociol Health Illn* 1982;**4**:167–82.

64. Cheng CCW, He WJA, Gouda H, Zhang MJ, Luk TT, Wang MP, *et al*. Effectiveness of very brief advice on tobacco cessation: a systematic review and meta-analysis. *J Gen Intern Med* 2024;**39**:1721–34.