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RESEARCH PAPER

A randomised controlled trial of the effect of automated interactive calling combined with a health risk forecast on frequency and severity of exacerbations of COPD assessed clinically and using EXACT PRO

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Abstract

Background: We have developed a winter forecasting service to predict when patients with COPD are at higher risk of an exacerbation and alert them via an automated telephone call.

Aims: To assess the effect of the service and its ability to predict periods of increased risk.

Methods: A 4-month prospective randomised controlled trial using clinical criteria and the EXACT PRO questionnaire to identify exacerbations. Patients were randomly allocated to receive alert calls. All patients completed a diary including the EXACT PRO questionnaire on a BlackBerry Smartphone each day. They were contacted and assessed if they appeared to be exacerbating.

Results: 79 patients participated, 40 received alert calls. The exacerbation frequency per patient per week was significantly greater during periods of predicted high risk (0.086±0.010 v 0.055±0.010). The exacerbation frequency (± standard error of the mean, SEM) in patients receiving alert calls was lower (0.95±0.27 v 1.17±0.29) but this was not statistically significant. Fewer patients receiving alert calls had one or more EXACT event compared to the controls (34% v 53%, p=0.11), their duration was shorter (8.2±2.0 v10.1±1.9 days, p=0.481) and they were less severe (AUC 65±21 v 115±22, p=0.118). There were no significant differences in the mean change (±SEM) in SGRQ scores between the groups.

Conclusions: The ability of the forecast to predict high risk periods was confirmed unequivocally. Alert calls appeared to reduce the frequency and severity of exacerbations but these effects did not reach statistical significance, perhaps because of the number of participants, lower than expected exacerbation rates, and the fact that there was contact with patients in both groups whenever they appeared to be exacerbating.

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Introduction

Delivering proactive care for exacerbations of chronic obstructive pulmonary disease (COPD) could offer many advantages over the traditional reactive approach, particularly as delaying therapy delays recovery.[1,2] Case management (i.e. the provision of proactive, coordinated care to people with complex health and social needs) has been proposed as a way of improving outcomes in COPD,[3] but identifying patients who will benefit is difficult and it does not reduce hospital admissions.[4]

There is a striking seasonality in the incidence of COPD exacerbations and meteorological factors appear to play a part in this. With clinicians, the UK Met Office has developed a unique and innovative health forecasting service (Healthy Outlook®) which comprises a rule-based forecasting model,[5] an interactive automated telephone calling system, and an anticipatory care package. The forecasting model is run weekly and aims to predict whether the risk of COPD exacerbations will be normal or increased in the next fortnight. If an elevated risk is predicted, automated calls are triggered which alert patients to the increased risk. At the beginning of the winter patients receive an information pack containing leaflets on COPD, thermometers to monitor the temperature in the bedroom and living room, and advice on recognising early symptoms of an exacerbation, managing their home environment, and keeping active. The automated call acts as a reminder for patients to follow this advice and to ensure they have sufficient medication.

Medical Research Council (MRC) guidance recommends that complex interventions should be evaluated using randomised controlled trials, using a sequential approach if necessary.[6] This prospective randomised trial had two aims:

- to assess whether the health forecasting system can predict periods of higher risk,
- and to assess the effect of the service on the frequency and severity of COPD exacerbations.

As well as identifying exacerbations using conventional clinical criteria, this is the first study to report the use of the EXACT PRO (Exacerbations of Chronic Pulmonary Disease Tool, Patient-Reported Outcome) questionnaire to identify COPD exacerbations in a clinical trial.

Methods

Study participants

All people aged over 40 with a diagnosis of COPD confirmed with spirometry (FEV_1 < 80% predicted, FEV_1/FVC ratio < 0.7) at three general practices in Devon, UK were invited to participate. Patients with a history of asthma or seasonal allergic rhinitis, other significant pulmonary disease, inability to use a BlackBerry Smartphone, or an exacerbation of COPD within four weeks of enrolment were excluded. All patients gave written informed consent. The study was approved by the Devon & Torbay Research Ethics Committee (ref 08/H0202/85).

Study design

This was a four month randomised single-blind study. During a one-week run-in period, patients completed daily diary questions displayed on the BlackBerry. Patients who successfully completed the trial period were entered into the study. Patients were allowed to continue taking all their usual medication and continued to receive usual care from their general practitioner (GP) and hospital specialists.

a) Baseline data

Smoking history, medication use, previous participation in an education or pulmonary rehabilitation programme, availability of antibiotics and steroids at home for treatment of exacerbations, and health status measured using the St George's Respiratory Questionnaire (SGRQ), were recorded. Nasal swabs were taken for viral analysis which will be reported elsewhere.

b) Alert calls

All patients received the Met Office information pack and a test call on their normal telephone to demonstrate how the system worked. Patients were then randomised either to receive the alert calls or not. An independent researcher who was not part of the study team used a list of binomial random numbers generated in block sizes of four to randomly allocate patients to receive or nor to receive alert calls from the automated system if an elevated risk of exacerbations was forecast. The investigators were unaware of which patients were allocated to receive the forecast and patients were not informed of their allocation.

Alert calls were made to the patient's normal telephone as occurs in the Healthy Outlook Service. The BlackBerry Smart Phones had their phone capabilities disabled and were only used for data collection and not to contact patients. The script for the alert call was successfully used in two pilot studies[7,8] and as part of the routine health forecasting service since 2007. Automated calls were made on Tuesday evenings, with up to two repeat calls if the first was not answered.

c) EXACT PRO

The Exacerbations of Chronic Pulmonary Disease Tool (EXACT) is a new validated patient-reported outcome (PRO) measure designed to standardise the method for evaluating the frequency, severity, and duration of exacerbations of COPD.[9-11] It is a 14-item daily diary and scores can range from 0-100, with higher scores indicating worse health state. Patients complete a daily diary comprising the EXACT questionnaire[9] plus additional questions on the colour of their phlegm, presence of symptoms of a cold or flu, whether they had seen a doctor or nurse that day for breathing problems or a cold, and whether they wanted the study team to contact them.

EXACT has been validated in a prospective, observational study in two groups of COPD patients: an acute group enrolled during a clinic visit for exacerbation and followed up for 60

days; and a stable group who had been exacerbation-free for at least 60 days.[10] The study showed that EXACT had internal consistenty (Cronbach's alpha 0.92) and was reproducible in stable patients (one-week intraclass correlation 0.77). EXACT scores differentiated acute and stable patients, scores improved over time in patients recovering from exacerbations, and differentiated between degrees of clinician-rated exacerbation severity. In addition, EXACT change scores differentiated responders and non-responders on Day 10, as judged by clinicians or patients.[10]

The diary questions were displayed on a BlackBerry Smartphone and the responses captured using the web-browsing capability in real time (Health Diary Inc., Toronto, Canada). The diary questions were delivered to the BlackBerry at 16.00 each day and patients were prompted to complete them that evening. A reminder was given the next day if no response was received, but submission was only allowed up to one day late.

d) Analysis of EXACT data

The developers have made initial recommendations about the identification of events using the diary, but this process continues to evolve and the nature of events identified by EXACT *vis a vis* clinical exacerbations is still being evaluated. The EXACT data were analysed according to the methods recommended by the developers at the time this analysis was performed (Leidy, personal communication).

Events were defined as an increase in total score of ≥12 points above baseline for at least two consecutive days, with the baseline recalculated every four weeks unless an event had occurred. The onset of an event was taken as the first day the score was elevated, and the end of the event was the point at which the score returned to within 6 points of baseline for three consecutive days. Severity was estimated using maximum EXACT score during an event and area under the curve (AUC).

e) Diary flags

The responses to a subset of diary items on breathlessness, cough, congestion and fatigue were used as a trigger to contact the patient to determine if an exacerbation was starting. The responses to this subset of questions were automatically analysed. If there had been an increase of ≥ 2 points in the mean of the summed raw daily scores for these items on the last two days compared to the mean of the summed item raw scores over the previous five days, an electronic flag was placed in the patient's study record.

The records were reviewed by a member of the study team each morning and patients with flags indicating they may be starting to exacerbate were contacted. If the telephone interview confirmed an exacerbation was starting, a home visit to collect further details and perform nasal swabbing was arranged. The nurses performing these visits were not aware of the patient's diary responses and, in an attempt to minimise clinical input that is not part of the usual service, they were encouraged not to offer clinical advice unless they had serious concerns about the patient's condition. This was clearly described in the protocol and approved by the ethics committee.

Outcome measures

The co-primary outcomes were the frequency of exacerbations defined using Anthonisen criteria[12] (see below) and the proportion of patients experiencing one or more exacerbation. Secondary outcomes were the ability of the forecast to predict an increased frequency of exacerbations in the 14-day period after an alert compared to the background rate, the frequency, severity and duration of events defined using EXACT, and changes in health status.

Exacerbations were classified by Anthonisen type. Type 1 exacerbations have increased dyspnoea, sputum volume and sputum purulence, type 2 have only two of these symptoms, and type 3 have one of these symptoms plus at least one minor symptom (upper respiratory infection in the last five days, fever without other cause, increased wheezing or cough, increased respiratory or heart rate). The number of hospitalisations was recorded.

Statistical analysis

Statistical analysis was undertaken using SPSS 15.0. The study was powered to identify a 30% reduction in the proportion of patients experiencing an exacerbation, assuming (on the basis of previous studies) that 90% of patients in the control group would exacerbate over the winter.

Exacerbation rates were compared using a negative binomial model to allow for inter-subject variability. The model took account of age, gender, smoking status, and baseline forced expiratory volume in one second (FEV_1).

The ability of the forecast to predict periods of increased risk was analysed using a mixed linear model at an individual patient level with the forecast as a fixed effect.

EXACT event rates were compared using a negative binomial model taking account of age, gender, smoking status, and baseline FEV_1. Differences between groups in the maximum EXACT score and the AUC during an event were analysed using a mixed linear model to take account of repeated observations in individuals.

Results

The full CONSORT statement is shown in Appendix 1 (available online at www.thepcrj.org).

Figure 1 shows patient flow and reasons for discontinuation. Approximately one third (240/679) of patients on the COPD registers of the practices expressed an interest in taking part in the study. 76 were not eligible, principally because of co-existent asthma, lack of spirometry data, or responding after recruitment had closed. 85 were not

Figure 1. Trial profile

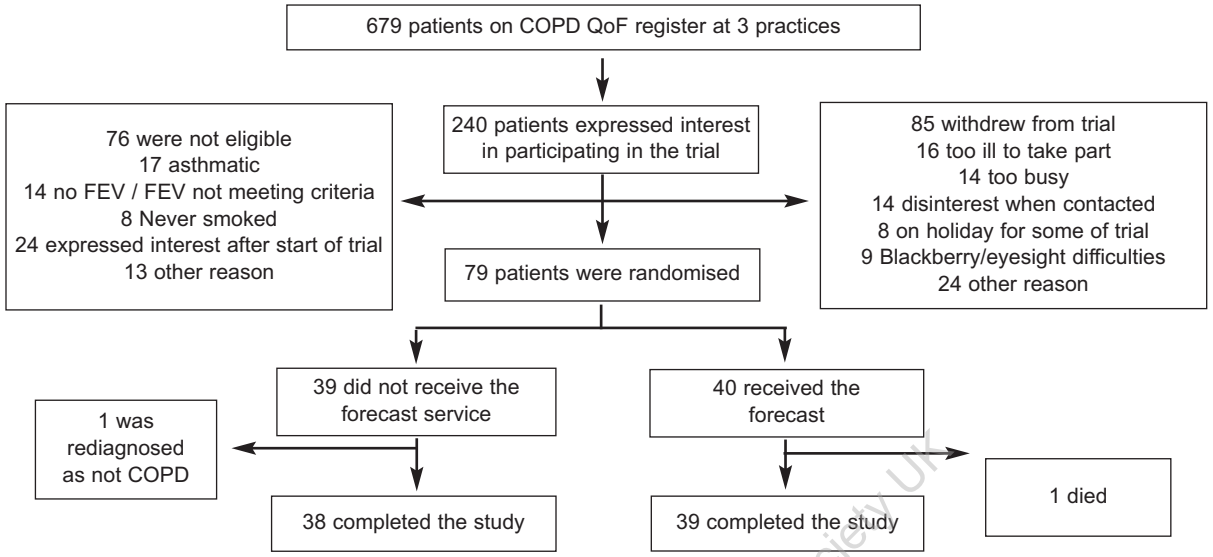

Table 1. Demographics and baseline characteristics

	Patients receiving forecast (n=40)	Patients not receiving forecast (n=39)
Age (years)	68.5 ± 1.5	70.2 ± 1.6
(range)	(48-88)	(49-86)
Male	29 (74.4%)	28 (73.7%)
Current smoker	12 (30.8%)	11 (28.9%)
Mean FEV_1 (l)	1.26 ± 0.08	1.42 ± 0.09
Mean FEV_1 (% pred)	48 ± 4	54 ± 3
Mean FEV_1/FVC ratio	0.48 ± 0.02	0.53 ± 0.02
Severity using NICE criteria		
Mild Airflow Obstruction	17 (43.6%)	25 (65.8%)
Moderate Airflow Obstruction	15 (38.5%)	9 (23.7%)
Severe Airflow Obstruction	7 (17.9%)	4 (10.5%)
Baseline SGRQ Score	52.4 ± 2.6	53.6 ± 2.4
COPD Management (Self Reported)		
Regular check-ups in primary care	30 (76.9%)	29 (76.3%)
Have attended education program	18 (46.2%)	13 (33.3%)
Have attended rehab/exercise program	17 (43.6%)	13 (33.3%)
Have a supply of antibiotics and or oral steroids at home	18 (46.2%)	13 (33.3%)
Visit respiratory specialist at hospital	16 (41.0%)	13 (33.3%)
Medication at baseline		
SABA	29 (74.4%)	29 (76.3%)
LABA	11 (28.2%)	3 (7.9%)
LABA/ICS	14 (35.9%)	20 (52.6%)
ICS	12 (30.8%)	16 (42.1%)
Oral Steroids	11 (28.2%)	9 (23.7%)
SAMA	14 (35.9%)	11 (28.9%)
LAMA	20 (51.3%)	14 (36.8%)

Data are mean (± standard error of the mean, SEM) or number (%)

(SGRQ – St Georges Respiratory Questionnaire, SABA – short-acting β_2-agonist, LABA – long-acting β_2-agonist, ICS – inhaled coticosteroid, SAMA – short-acting muscarinic antagonist, LAMA – long-acting muscarinic antagonist)

Table 2. Details of forecast calls

Date of call alert	Number of participants called	Number of participants reached	Number of patients indicating worse symptoms or shortage of medications in response to call
22/12/2008	39	25	8
05/01/2009	39	31	14
02/02/2009	39	32	7
02/03/2009	39	34	16

randomised after assessment, principally because they lacked time or interest or because they were considered too ill. Only nine people were not randomised because they were unable to use the BlackBerry. 79 patients were randomised, with 40 in the intervention arm and 39 as controls. Two patients did not complete the trial. The two groups were generally well matched (see Table 1); however, more patients in the group receiving alert calls had attended a COPD education or exercise/rehabilitation programme and more controls were receiving ICS/LABA therapy.

Overall compliance with the BlackBerry was very high at 95.4%, with little difference between the two groups (94.3% for controls and 96.3% for intervention). The average number of missed days was 4.9 (SD 7.2) out of 107.

During the trial period (from 14th December to 31st March) there were four alert calls on 22nd December, 5th January, 2nd February and 2nd March. These calls were made to patients' normal telephones and on average 78% of patients were successfully contacted (Table 2).

Exacerbations

86 exacerbations occurred in the 79 patients. 32 were Anthonisen type 1, 24 were type 2, and 27 were type 3. Three were characterised by a marked increase in breathlessness and were regarded as an exacerbation by the patient when contacted but did not fall into an Anthonisen category as there were no other symptoms. Three patients were hospitalised for exacerbations (two in the group that received the forecast).

Table 3. Number of patients with different numbers of exacerbations (defined clinically) during the trial

	Number of exacerbations				
	0	1	2	3	4
Patients not receiving forecast	12	11	11	4	0
Patients receiving forecast	16	10	9	3	1

58% of the patients in the group receiving the forecast experienced one or more clinical exacerbation compared with 68% in the control group (see Table 3). The exacerbation frequency (± standard error of the mean, SEM) over the trial period in those receiving the forecast was 0.95±0.27 and 1.17±0.29 in the controls (p=0.52).

Accuracy of the forecast

54 exacerbations (62%) occurred within 14 days of an alert call, and 33 (38%) within seven days. The exacerbation frequency per patient per week was significantly greater in the 14-day period following an alert call than the frequency during other periods (0.086±0.010 v 0.055±0.010, p = 0.035). The frequency was particularly increased in the 7-day period following an alert call compared to other periods (0.101±0.015 v 0.061±0.008, p = 0.018).

EXACT scores

There was no difference in mean EXACT scores at baseline or during the last week of the study between the two groups (see Table 4).

34% of the patients in the group receiving the forecast experienced one or more EXACT exacerbation compared with 53% in the control group, and the distribution of EXACT exacerbation frequencies is shown in Table 5. There was no difference between the groups in the rate of events defined on the basis of changes in EXACT scores or in the maximum EXACT scores reached during events. The mean duration of the event was two days less and the AUC for EXACT scores

Table 4. EXACT results

	Patients receiving forecast n=40	Patients not receiving forecast n=39	p
Mean baseline EXACT ± SEM	40.2 ±1.67	39.6 ± 1.8	0.997
Mean EXACT during last week of study ± SEM	38.2 ± 1.8	35.9 ± 2.0	0.983
Mean event rate ± SEM	0.48 ± 0.15	0.55 ± 0.17	0.724
Max EXACT score during event ± SEM	52.5 ± 3.7	60.2 ± 3.6	0.150
Mean event duration (days) ± SEM	8.2 ± 2.0	10.1 ± 1.9	0.481
Mean AUC during event ± SEM	103 ± 31	148 ± 30	0.295

Table 5. Number of patients with different numbers of exacerbations (defined using EXACT) during the trial

	Number of exacerbations				
	0	1	2	3	4
Patients not receiving forecast	17	14	3	2	0
Patients receiving forecast	25	10	1	2	0

during an event was less in the group receiving the alert calls (Table 4) – but these differences were not statistically significant.

There is preliminary evidence to suggest that using EXACT scores the severity of events can be interpreted according to the maximum score reached as follows: < 45 – mild, 45-54 moderate and > 55 severe. (Leidy, personal communication). In people not receiving the alert calls 13.6% of events were mild, 27.3% moderate and 59.1% severe, whereas in people receiving the calls 36.4% were mild, 27.3% moderate and 36.4% severe (p=0.177, Chi-squared).

Health status

There were no significant differences in the total SGRQ scores at the end of the study (49.7 ± 2.4 in those receiving the forecast and 51.5 ± 2.4 in controls).

Discussion

COPD exacerbations worsen lung function and health status and cause considerable mortality.[13,14] They are one of the commonest reasons for hospitalisation,[1] and admission rates increased by nearly 30% between 2001 and 2005.[15] Exacerbations may be triggered by bacterial and viral infections as well as other environmental factors including changes in weather and air pollution. Exacerbations triggered by respiratory viral infections are more severe and are associated with longer recovery times than those triggered by other factors.[16,17]

Current strategies to reduce exacerbation rates include optimising pharmacotherapy, using oxygen when appropriate and vaccination,[18] and prompt oral corticosteroids can shorten the duration of an exacerbation.[19] Proactive care using case management does not reduce admission rates.[4] This may be because most admissions involve patients who would not be considered at high risk.[20] Therefore, new approaches are needed. Automated interactive telephone calls triggered by a health risk forecast are an innovative method for delivering proactive care on a large scale. Telephone follow-up of patients with respiratory disease is feasible and effective,[21-24] and automated interactive calling has been used successfully in the management of heart failure[25] and asthma,[22,26] and in monitoring patients with COPD.[27]

Previous evaluations of the Met Office COPD Health Forecast Service using historical comparisons have suggested that it is effective at reducing hospitalisation rates. This study is the first prospective assessment of the service and shows conclusively that the forecast can predict periods of increased risk. COPD exacerbations were twice as common during periods of predicted high risk. This two-week period encompasses the 10-day interval between virus acquisition and maximal chest symptoms seen in a virus challenge model of COPD exacerbations.[28]

This study also suggests that alert calls have the potential to reduce the frequency, duration and severity of exacerbations; however, although trends were seen, none of the differences reached statistical significance. The rate of exacerbations observed in the control group was lower than the expected value used in the protocol power calculation (68% v 90%). Thus, although the final sample size of 79 was only just short of the 82 needed according to the power calculation, a larger sample size may have yielded clearer results. However, we believe that the lack of statistical significance also reflects the difficulty of undertaking a study using a methodology that included patient contact when the intervention itself was a triggered patient contact. This issue was considered during the design of the study but no way of resolving it satisfactorily could be found. The results may also have been affected by other factors such as the fact that more patients receiving the forecast had participated in education/pulmonary rehabilitation programmes leaving less room for improvement, and greater use of ICS/LABA combination inhalers (which reduce exacerbation rates) in the control group may also have contributed to the lack of a clear effect of the forecast[29] in the control group. A further issue may be the fact that not all alert calls were answered by patients. Although the service generates up to two repeat calls if the first is not answered and patients are asked to give the phone number on which they would prefer to be contacted (either land line or mobile), one in five calls were not answered and thus these patients were not aware of the increased risk and able to respond to the forecast.

This is the first study to report the use of EXACT PRO to track exacerbations in a clinical trial. The participants did not have any difficulty completing the questionnaire using the BlackBerry. The results support the validation studies and show that it can differentiate acute and stable patients and can be used to assess the severity and duration of exacerbations.[9,10] Review of EXACT PRO scores for individual patients showed that in some cases there was a secular trend in the mean score over time, both up and down, which had the potential to affect the identification of the start and end of events when using the criterion of a change from baseline. Nevertheless, EXACT PRO did appear able to detect exacerbations and give information about their severity and duration. Further analysis is being undertaken to examine the relationship between exacerbations confirmed using clinical criteria and those events identified by changes in EXACT scores. The developers are also still refining the methods recommended for the analysis of EXACT PRO.

The 2009 Annual Report of the Chief Medical Officer for England stated that "there are clear benefits in communicating directly with people when they are at increased risk of becoming unwell – given the right information at the right time, individuals are better able to self manage their health".[30] Health forecasts allow preventive health measures to be targeted to vulnerable groups at the right time. To be clinically useful it is important that the forecasts are delivered to large numbers of patients in a timely fashion. This study shows that automated calling as part of a health forecast service is feasible.

The Healthy Outlook service combines the alert calls with an information pack which provides patients with important useful information about their condition, as well as thermometers to monitor the temperature in the bedroom and living room, and advice on recognising early symptoms of an exacerbation. The alert calls remind people of this advice at times of increased risk, particularly the importance of checking they have enough medication, ensuring they wear warm clothing when going out, monitoring the temperature in their home more closely, and avoiding unnecessary trips outdoors. Previous work has shown that nearly 90% of people receiving alert calls felt that they provided an important reminder at times when the prevailing weather conditions might present an increased risk to their health; one third of patients reported that they had sought a repeat prescription as a result of receiving an automated call, and one in five indicated they took some other remedial action such as turning on their heating, obtaining extra supplies of food, or avoiding unnecessary trips outdoors.[31]

By encouraging behaviours such as staying at home or keeping warm, the alert call may reduce exacerbation rates by reducing the risk of acquiring infections,[32] the most common triggers.[33,34] However, the forecast and alert call may potentially have a greater role in reducing the impact of infections by ensuring that patients have sufficient medication and reminding them of the importance of prompt treatment.[2]

Qualitative data show that people receiving the forecast service felt empowered by it, and as a result had a sense of control over their condition as well as making them feel cared for.[31] These data also indicate that it is most beneficial for those who are ready to act in response to the automated calls, suggesting that when using the service in routine practice offering it to patients on an `opt-in' basis is likely to be the most successful way of implementing it.

This study shows consistent effects on the frequency, duration and severity of exacerbations but the differences were not statistically significant. As well as the factors discussed above, this may also reflect the relative lack of potency of acute interventions to prevent exacerbations or reduce their severity. If more effective therapies for treating exacerbations become available the combination of the forecast with automated interactive calling is an efficient way of supporting their use; this approach offers a new and exciting way of delivering proactive care to large numbers of patients with long term conditions.

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Conflicts of interest

David Halpin chairs and Mark Levy is a member of the MetOffice Health Forecasting Advisory Group. They have no financial interest in the MetOffice. Tish Laing-Morton, Sarah Spedding & Penny Marno are employees of the MetOffice. Jonathan Lewis and Paul Newbold are employees of AstraZeneca. Peter Coyle has no conflicts of interest to declare. Mark Levy is the Editor Emeritus of the *PCRJ*, but was not involved in the editorial review of, nor the decision to publish, this article.

Contributorship

David Halpin, Mark Levy, Penny Marno, Tish Laing-Morton, Jonathan Lewis, Paul Newbold & Peter Coyle all contributed to the design of the study. David Halpin, Penny Marno, Tish Laing-Morton, & Sarah Spedding carried out the study. David Halpin & Penny Marno analysed the data. David Halpin & Penny Marno wrote the first draft of the manuscript and all authors contributed to the final draft. David Halpin acts as guarantor of the data.

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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	1-2
	2b	Specific objectives or hypotheses	2
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	2
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Not Applicable
Participants	4a	Eligibility criteria for participants	2
	4b	Settings and locations where the data were collected	2
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	2-3
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	3
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Not Applicable
Sample size	7a	How sample size was determined	3
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Not Applicable
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	2
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	2
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	2
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	2
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	2

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	2
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	3
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	3-4
	13b	For each group, losses and exclusions after randomisation, together with reasons	4 + fig 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	2
	14b	Why the trial ended or was stopped	Not Applicable
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	3
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	5
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Not Applicable
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Not Applicable
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	6-7
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	6-7
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	6-7
Other information			
Registration	23	Registration number and name of trial registry	1
Protocol	24	Where the full trial protocol can be accessed, if available	Not available
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	7

We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.