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Long-acting dual bronchodilator therapy (indacaterol/glycopyrronium) versus nebulized short-acting dual bronchodilator (salbutamol/ipratropium) in chronic obstructive pulmonary disease: A double-blind, randomized, placebo-controlled trial

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A B S T R A C T

Introduction: Most guidelines recommend long-acting bronchodilators over short-acting bronchodilators for patients with chronic obstructive pulmonary disease (COPD). The available evidence for the guidelines was based on dry powder or pressurized metered dose inhalers, but not nebulizations. Nevertheless, there is considerable, poorly evidenced based, use of short acting nebulized bronchodilators.

Methods: This was an investigator initiated, randomized, active controlled, cross-over, double-blind and double-dummy single centre study in patients with stable COPD. The active comparators were indacaterol/glycopyrronium 110/50 μg as Ultibro® via Breezhaler® (IND/GLY) and salbutamol/ipratropium 2,5/0,5 mg via air driven nebulization (SAL/IPR), both given as a single dose on separate days. The primary end point was the area under the FEV_1 curve from baseline till 6 h. Secondary end points included change in Borg dyspnoea score, adverse events and change in hyperinflation measured by the inspiratory capacity.

Results: A total of 33 COPD patients completed the trial and were evaluable, most of them were ex-smokers. The difference between the tested regimens for the primary endpoint, FEV_1 AUC 0–6 h, 2965 ± 1544 mL (mean ± SD) for IND/GLY versus 3513 ± 1762 mL for SAL/IPR, was not significant (P = 0.08). The peak in FEV1 was higher and was reached faster with SAL/IPR compared to IND/GLY. No other significant differences were detected for the secondary endpoints including the Borg score, or adverse events.

Conclusion: Among patients with stable COPD, dry powder long-acting single inhalation of a LABA and a LAMA (IND/GLY) was not superior compared to nebulized short-acting salbutamol plus ipratropium (SAL/IPR) in its bronchodilating effects over 6 h.The effects of the nebulization kicked in faster and peaked higher. The observed differences may be caused by the difference in dosing between the two regimens. The improvement in Borg dyspnoea score did not favour the nebulization. Long-term outcomes were not assessed in this study.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable disease that is characterized by persistent airflow limitation and respiratory symptoms. The obstruction is partially reversible in many patients, but (by definition) not fully so. Hence, the cornerstone of treatment is bronchodilation [1].

Inhaled bronchodilators are available in short- and long-acting forms, and can be administered via dry powder inhalers, pressurized metered dose inhalers, or nebulizations [2]. The most robust data on effectiveness and efficacy of bronchodilators, and also with the longest follow-up time, is available for long-acting bronchodilators. They provide sustained improvements in obstruction, symptoms, health related quality of life, and exacerbation rates versus no bronchodilation and versus the short-acting forms [1,3,4]. Additionally, combined long-acting bronchodilators appear superior to single long-acting ones [5].

In balance, when affordable, use of long-acting drugs frequently in combination is evidence based and frequently prescribed to new patients. Indeed, the Global Initiative for Obstructive Lung Disease recommends maintenance dosing of long-acting bronchodilators over short-acting ones for all severities but the most mild severity of COPD (group A) for which no recommendation is provided regarding the duration of action [1].

There is considerable use of nebulized bronchodilators, of which

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Abbreviation list

COPD	chronic obstructive pulmonary disease
IND/GLY	indacaterol/glycopyrronium
SAL/IPR	salbutamol/ipratropium
AUC	area under the curve
BMI	body mass index
FEV_1	post-bronchodilator forced expiratory volume in 1 s
IC	inspiratory capacity
TLC	total lung capacity
RV	residual volume
R_{AW}	Airway Resistance
DLCOsb	single breath diffusing capacity for carbon monoxide
LABA/LAMA	long-acting β_2-agonist (LABA)/long-acting muscarinic antagonist (LAMA)
SABA/SAMA	short-acting β_2-agonist (SABA)/short-acting muscarinic antagonist (SAMA)

mainly short-acting forms exist, even though there is little evidence to support this. Almost all above mentioned comparisons were based on either dry powder inhalers or pressurized metered dose inhalers, but not on nebulizations [4]. Reasons for their use include especially patient preference, next to costs, ease of inhalation technique in severely sick people, and perhaps: old routines [6,7]. The lack of real data and the fact that many patients are so happy with their nebulizer were good reason to compare nebulization of short-acting bronchodilators to combined long-acting bronchodilators in dry powder formulation. We hypothesized that the bronchodilating effect would be greater with the long-acting drugs compared to nebulization of short-acting bronchodilators, at no cost of lesser effect on dyspnea.

In the present study, single dose long-acting single inhaler indacaterol plus glycopyrronium (IND/GLY) as dry powder is compared with combined short-acting salbutamol plus ipratropium (SAL/IPR) via nebulizer in patients with COPD in stable state. We compared the therapies in terms of FEV_1 and symptoms of dyspnoea over a period of 6 h.

2. Methods

2.1. Trial design

We conducted an investigator initiated, randomized, active control, cross-over, double-blind and double-dummy single centre study at the University Medical Center Groningen, the Netherlands. The active comparators were indacaterol/glycopyrronium 110/50 μg dry powder as Ultibro® via Breezhaler® and ipratropium/salbutamol 0,5/2,5 mg via air driven nebulization.

The primary end point was the area under the curve from baseline till 6 h for the FEV_1 (percent predicted and ml). Secondary end points included change in dyspnoea symptoms measured by the Borg score, over the same period, as well as change in hyperinflation measured by the inspiratory capacity, and (time to) peak effect. Additionally, adverse events were assessed during the trial.

2.2. Patients

The main inclusion criteria were an age of at least 40 years with a diagnosis of COPD and a post-bronchodilator FEV_1 below 80% predicted. COPD was defined as a physician diagnosis and an FEV_1/FVC ratio of less than 0.70 after bronchodilation. Main exclusion criteria were asthma, chronic hypoxaemia, and the occurrence of a COPD exacerbation in the six weeks before inclusion. Maintenance concomitant inhaled corticosteroids were allowed during the whole trial, in stable dose.

The study was approved by the local medical ethics committee (Medisch Ethische Toetsingscommissie UMC Groningen, number METc2015/113), all patients provided written informed consent, and the study was registered at clinical trials.gov (NCT02576626).

2.3. Procedures

In patients meeting the inclusion but not the exclusion criteria all prior bronchodilators were withheld, and patients were switched to fenoterol/ipratropium 50/20 μg by pressurized metered dose inhaler as needed for a washout period of 7 days. At the end of this washout period patients were randomized 1:1 to either arm A or B. Randomization was conducted with the use of block sizes of four without stratification. Patients in arm A received a single dose of dry powder indacaterol/glycopyrronium (110/50 μg) + placebo nebulization, followed after a washout period of 7 days by a single dose ipratropium/salbutamol (0.5/2.5 mg) nebulization and placebo Breezhaler. Patients in arm B had the reverse order.

The last dose of open label fenoterol/ipratropium was permitted till 6 h before the measurements and administration of the single dose study drugs. Spirometric values, inspiratory capacity and Borg score were measured according to the ATS/ERS criteria during both visits at approximately the same time of day and by the same team of spirometrists on the same apparatus (Jaeger, CareFusion). Diffusion and lung volumes at baseline were measured with a Jaeger MasterScreen, CareFusion [8]. After the baseline measurement of each study visit, at T = 0 min the patient started with the Breezhaler (double dummy, so active or placebo). Nebulization (double dummy as well) started immediately after the Breezhaler was taken. Incidences of adverse events and serious adverse events were registered at each visit. Patients and trial staff remained blinded till after the database lock. Measurements were performed at baseline (T0) and at 15, 30, 60, 120, 240 and 360 min.

2.4. Statistical analyses

A power calculation was performed for both the area under the curve (AUC) of the FEV1 and the Borg score. We used an alpha of 0.05 and a power of 90%. The estimated difference was extrapolated based on the known MCID of FEV1 and BORG for one time point. In a cross-over study aiming at superiority, with a two-tailed test this required a total sample size of 34 evaluable patients for the AUC of the FEV_1 and for the Borg score 30 patients.

Data was analysed with IBM SPSS 24. Differences between the outcome measurements of the two treatments were assessed with paired t tests. The area under the curve (0–6 h) was pre-specified as primary endpoint for the FEV_1, since this was deemed to reflect the mean effects for an individual with COPD better than any single measurement at a fixed time. The FEV_1 as percentage predicted was used based on the reference values by Quanjer et al. [9] Changes in Borg scores were tested with paired t-tests. A p value of <0.05 was considered significant.

2.5. Results

Between September 2015 and August 2017 53 patients were screened of whom 39 were included in the trial. Of those included, 33 completed the trial and were deemed evaluable (Fig. 1).

Mean ± SD age was 69 ± 6 yrs and post-bronchodilator FEV_1 was 59% ± 14% predicted. Baseline characteristics for the evaluable patients are shown in Table 1. Most patients were ex-smokers, 1 never smoked and 1 was an active smoker.

2.5.1. Pulmonary function

The primary endpoint, FEV_1 AUC 0–6, showed a non-significant difference in favour of the SAL/IPR regimen: 2965 mL ±1544 (mean ± SD) for IND/GLY versus 3513 mL ±1762 for SAL/IPR respectively (P

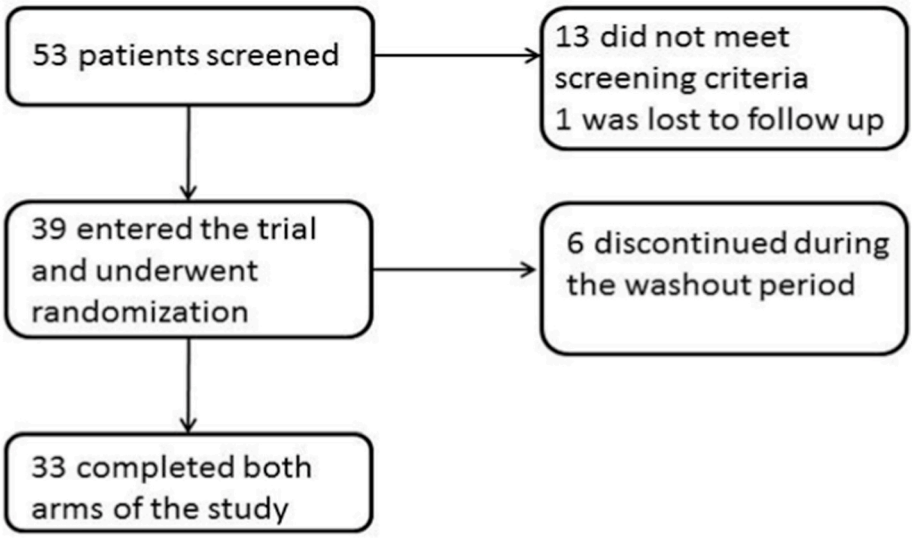

Fig. 1. Flowchart of the study.

Table 1
Baseline characteristics of the patients (n = 33).*

Age (yr)	69 ± 6
Gender (male, %)	26 (78.8)
BMI	29.5 ± 5.9
Pack years	51.8 ± 40
Borg score	1.5 ± 1.4
COPD exacerbations last year**	Median 0, Range 0-2
FEV_1 (liters)	1.73 ± 0.45
FEV_1 (% of predicted)	59 ± 14
IC (liters)	2.96 ± 0.69
TLC (liters)	7.62 ± 1.58
TLC (% of predicted)	114 ± 19
RV (liters)	3.41 ± 0.99
RV (% of predicted)	136 ± 38
R_{aw} (kPa/L/s)	0.36 ± 0.13
DLCOsb (mmol/kPa)	5.86 ± 2.04
DLCOsb (% of predicted)	67 ± 23

* Table 1. Baseline Characteristics of the patients. Data are presented as means ± standard deviation unless otherwise indicated.

** COPD exacerbation (treated with either prednisolon and/or antibiotic course) in the last 12 months. BMI: Body mass index, FEV_1: post-bronchodilator forced expiratory volume in 1 s, IC: inspiratory capacity, TLC: total lung capacity, RV: residual volume, R_{AW}: Airway Resistance DLCOsb: single breath diffusing capacity for carbon monoxide.

= 0.08) (Fig. 2).

No differences were found in change in inspiratory capacity from baseline (Fig. 3):

2.5.2. Dyspnoea

No significant differences were detected in the key secondary endpoint, change in Borg dyspnoea score from baseline (Fig. 4).

2.5.3. Peak effect

The peak effect of FEV_1 (L) was 0.32 L (SE: 0.02 L) with IND/GLY, and 0.39 L (SE: 0.03 L) with SAL/IPR (P = 0.01). The time till reaching this peak effect for the FEV_1 was 176 min (SE: 19) with IND/GLY and 107 min (SE: 12 min) with SAL/IPR (P < 0.01).

2.5.4. Adverse events

No serious adverse events were reported in this short running trial. Six patients did not complete the trial due to mild and moderate adverse events. Most events occurred during the washout periods; two due to COPD exacerbations not requiring hospitalization, one because of palpitations and dyspnoea as a side effect of the fenoterol/ipratropium, one due to fenoterol/ipratropium intolerance, not further specified, and two patients did not complete the study due to increased dyspnoea. Six of those who finished the study reported seven other adverse events. One patient reported coughing after inhalation of IND/GLY. There were no other differences in adverse effects reported relative to treatment sequence. Unrelated to the trial medication were reported spinal arthrosis, a COPD exacerbation, worsening mucus production, atypical chest pain, increased dyspnoea when without additional bronchodilator, and hoarseness.

3. Discussion

This clinical trial showed no significant difference between long-acting indacaterol/glycopyrronium dry powder in a single inhalation and short-acting salbutamol plus ipratropium via nebulizer, in FEV_1 in the first 6 h after inhalation in patients with stable state COPD. The peak in FEV1 was higher and was reached faster in the SAL/IPR compared with the IND/GLY. There was no difference in improvement in Borg dyspnoea score, the key secondary endpoint. No other differences were detected for the other secondary endpoints or adverse events.

In stable COPD, strategy documents recommend the use of long acting bronchodilators as opposed to short-acting bronchodilators, since the maintenance use of LABA/LAMA prevents the occurrence of exacerbations and provides more bronchodilation and symptoms relief compared to SABA/SAMA [1]. Improvements in lung function are associated with improved long term outcomes and quality of life [10–12]. During exacerbations however, when patients tend to suffer from more dyspnoea and hyperinflation many physicians tend to treat COPD with fast and short acting bronchodilators [13–15]. Importantly, many patients favour the use of nebulized bronchodilators during acute exacerbations and sometimes also in stable state with more severe disease [16].

No previous comparisons between indacaterol/glycopyrronium and nebulized salbutamol/ipratropium were published. The current study shows an earlier onset of action and greater peak in the nebulized salbutamol/ipratropium treatment, probably contributing to patient preferences for nebulized treatment. The curve suggests that in the long term a more stable bronchodilation effect can be obtained with single dose indacaterol/glycopyrronium. However, in future research these results should be confirmed for this single dose situation. And more importantly, the observation should be extended to multiple dose maintenance.

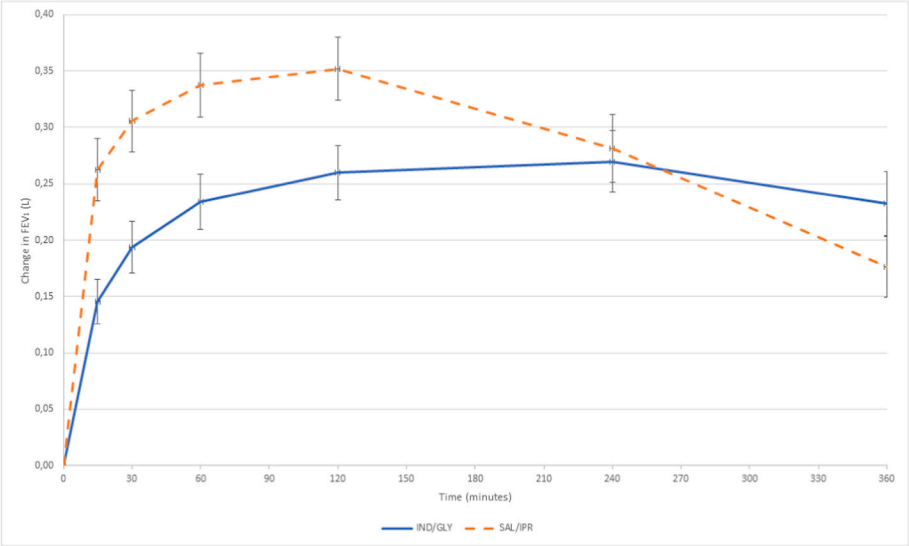

Fig. 2. Shows the change in liters of the FEV_1 with indacaterol/glycopyrronium versus the salbutamol/ipratropium. The primary end point was area under the curve 0–6 h (P = 0.08). Error bars represent the standard error.

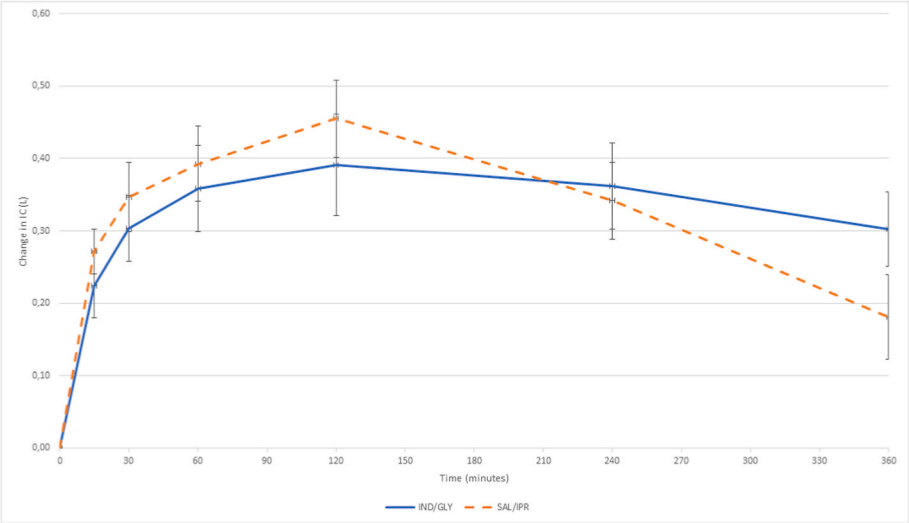

Fig. 3. Shows the change in liters of the IC with indacaterol/glycopyrronium versus salbutamol/ipratropium. No significant differences were observed. Error bars represent the standard error.

We had not expected the faster onset of action with salbutamol/ipratropium compared to indacaterol/glycopyrronium given the literature suggesting an onset of action within 5 min for both indacaterol and glycopyrronium, at least comparable to salbutamol and much better than of ipratropium [17,18].

An important hurdle we could not overcome with the study design was the difference in dosing: the nominal dose of salbutamol/ipratropium is deemed of higher potency than 110/50 μg indacaterol/glycopyrronium, even though a good dose equivalency ratio has not been established in the literature.

Many patients are happy with nebulizers, usually experiencing reduction of dyspnoea especially during an exacerbation. The faster onset of action and higher peak of the improvement in FEV_1 with the nebulized SAL/IPR was paralleled by the suggestion of a slightly greater early dyspnoea reduction at 30 min, with by contrast slightly smaller dyspnoea reduction at 6 h. These findings do not explain well the patient preference for nebulization. Alternative explanations include easy inhalation of nebulization, and total rest for longer period while inhaling via the nebulizer. Finally, there is a clear well perceived deposition of drug, even though this is at the unwanted oropharyngeal site.

Potential limitations of the study, next to the mentioned potency inequality, are that it was powered to detect superiority only. Therefore, it is not possible to make firm statements about equivalency. Next the study was slightly underpowered by one patient. Due to pharmacological arguments the authors deem any carry-over effect of the medication as highly unlikely due to the 7 days washout periods prior to the measurements. This long washout period with only fenoterol/ipratropium treatment (mostly by stopping long-acting bronchodilators during the study) may have caused the relative high number of dropouts. Since this study did not collect data on any outcomes later than 6 h after medication intake, it is important to limit the interpretation of the results to this period only.

Strong points of the study included the double-dummy design as opposed to most studies so far assessing the effects of nebulizers versus for instance metered dose inhalers in unblinded fashion. The cross-over design has the advantage of each patient being his own control, which is especially valuable for the Borg score measurements. Finally, the consistency across primary and secondary endpoints also lends credibility.

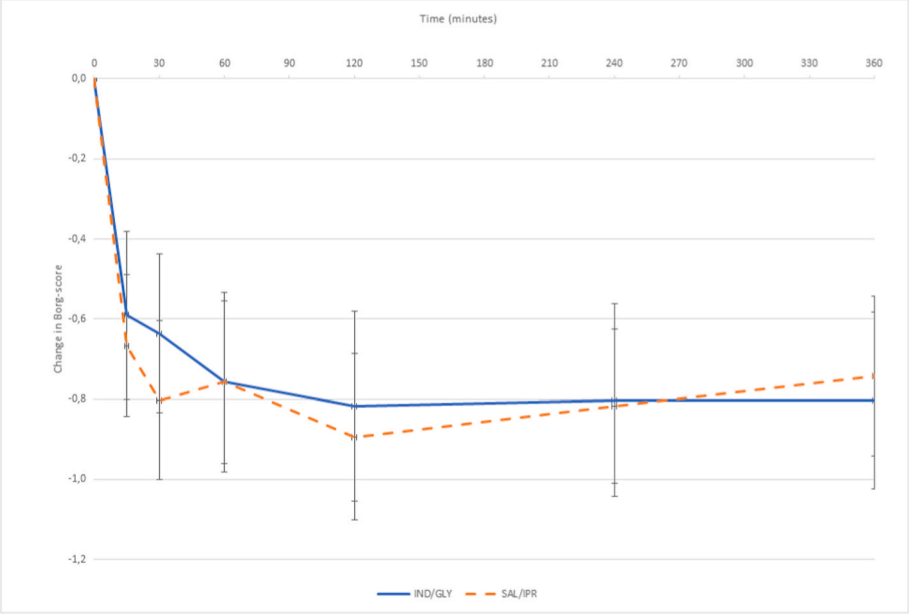

Fig. 4. Shows the change in Borg dyspnoea score with indacaterol/glycopyrronium versus the salbutamol/ipratropium. No significant differences were observed. Error bars represent the standard error.

This study was in patients with stable state COPD and a mean FEV_1 of 59% pred. Whether similar outcomes would be found in patients with more severe disease remains to be established. Additionally, long-acting bronchodilators are routinely used once or twice a day, leading to larger cumulative effects then single dosing, an effect not taken in to account in this single dosing study [19,20]. It might be of interest to investigate whether nebulized long-acting drugs are equivalent to the same drugs and dose via a metered dose inhaler or a dry powder device for patients with an impaired inhalation technique.

Treatment of patients during an exacerbation will be an important additional research direction: it will be interesting to study whether the long-acting effects of the LAMA/LABA can also be effective and fast acting in the more acute setting of in-hospital exacerbation treatment.

In conclusion, we found that among patients with stable COPD, long-acting single inhalation of a LABA and a LAMA was not superior compared with short-acting salbutamol plus ipratropium via nebulizer in its bronchodilating effects or in the reduction of dyspnoea in the first 6 h after administration. The different potencies of the formulations were too great a challenge to overcome. Future studies include a similar study in the acute situation, i.e. during an exacerbation, and preferably with nebulized long-acting drugs which are now available in some countries.

Role of the funding source

The study was investigator initiated; the investigators were responsible for the design and analysis of the study, oversaw its conduct and wrote the study report. Novartis Pharma B.V. provided an unrestricted research grant, as well as raw data to aid the power calculations. The funder was not involved in either data gathering, analysis, or writing of the study report. The funder had no access to the data of the study. WG and HK had final responsibility for the decision to submit for publication.

Data sharing

Individual deidentified participant data (including data dictionaries) will be shared: yes. What data in particular will be shared: spss files and support with the analysis from author team if needed. When the data will become available and for how long: immediately till the end of the data storage period as is regulated by Dutch Laws. By what access criteria data will be shared: by submitted and then approved protocol by the current trial authors.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: OC, LW, DS, AN, and JV have nothing to disclose. WG: reports research grant from Novartis paid to his institution. HK reports research grants from GSK, Novartis, and Boehringer, and fees for consultancies in advisory boards from other from GSK, Novartis, and Boehringer, all paid to his institution.

CRediT authorship contribution statement

Wouter H. van Geffen: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing - original draft. **Orestes A. Carpaij:** Project administration, Resources, Writing - review & editing. **Lotte F. Westbroek:** Project administration, Resources, Writing - review & editing. **Dianne Seigers:** Project administration, Resources, Writing - review & editing. **Alice Niemeijer:** Project administration, Resources, Writing - review & editing. **Judith M. Vonk:** Methodology, Supervision, Validation, Writing - review & editing. **Huib A.M. Kerstjens:** Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Validation, Writing - review & editing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2020.106064.

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