Cost-effectiveness of as-needed budesonide-formoterol in adults with mild asthma: the Novel START trial

William Leung[1,2,3], Helen K. Reddel[4,5,6], Tiffany Hung[7], Mark Weatherall[1], Ilka Pelzer[8], Mark Holliday[3], Trudy Sullivan[9], Tim Harrison[10,11], Ian D. Pavord[12], Michael G. Baker[1], Stefan Ebmeier[3,13], Alberto Papi[14], Richard Beasley[3,15] and Robert J. Hancox[9,16]

[1]University of Otago Wellington, Wellington, New Zealand. [2]Department of Medicine, University of Auckland, Auckland, New Zealand. [3]Medical Research Institute of New Zealand, Wellington, New Zealand. [4]Woolcock Institute of Medical Research, Macquarie University, Sydney, Australia. [5]Macquarie Medical School, Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney, Australia. [6]Sydney Local Health District, Sydney, Australia. [7]Cardiff Business School, Cardiff University, Cardiff, UK. [8]Lübeck University of Applied Sciences, Lübeck, Germany. [9]Department of Preventive and Social Medicine, University of Otago, Dunedin, New Zealand. [10]Nottingham NIHR Biomedical Research Centre, University of Nottingham, Nottingham, UK. [11]AstraZeneca PLC, Global Medical Affairs, Cambridge, UK. [12]Oxford Respiratory NIHR BRC, Nuffield Department of Medicine, University of Oxford, Oxford, UK. [13]Division of Infectious Diseases, Imperial College London, London, UK. [14]Respiratory Medicine Unit, Department of Medical Sciences, Università di Ferrara, Ferrara, Italy. [15]Capital, Coast, and Hutt Valley District, Te Whatu Ora (Health New Zealand), Wellington, New Zealand. [16]Department of Respiratory Medicine, Waikato Hospital, Hamilton, New Zealand.

Corresponding author: William Leung (william.leung@otago.ac.nz)

Shareable abstract (@ERSpublications)
In mild asthma, budesonide-formoterol as needed is cost-saving for the health system, patient and society compared to maintenance budesonide with salbutamol reliever, and it is cost-saving from a societal perspective compared to salbutamol reliever alone https://bit.ly/4lddSDQ

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Abstract

Background The Global Initiative for Asthma recommends as-needed combination inhaled corticosteroid-formoterol reliever for mild asthma. Its cost-effectiveness is uncertain outside double-blind regulatory trials. The study objectives were to assess the cost-effectiveness of as-needed budesonide-formoterol *versus* maintenance budesonide plus as-needed salbutamol, and *versus* as-needed salbutamol, in averting exacerbations in adults with mild asthma during 12-month follow-up of the New Zealand participants (n=551) of the open-label Novel START multicountry clinical trial.

Methods New Zealand health-system and societal perspectives were adopted using 2025 resource costs. Healthcare utilisation comprised electronically monitored inhaler use (with multiple imputation for missing data), asthma-related pharmaceuticals, primary-care visits, emergency-department visits and hospitalisations. Regression methods were used for cost-effectiveness analysis. Scenarios included generic substitution and prescription-charge exemption.

Results As-needed budesonide-formoterol, compared with maintenance budesonide plus as-needed salbutamol, is more effective at reducing severe exacerbations and provides an annual health-system cost saving of NZD 12 (95% CI 0–28) per patient, increasing to NZD 22 (95% CI −15–58) if a societal perspective is adopted. Compared with as-needed salbutamol alone, as-needed budesonide-formoterol costs the health system NZD 38 and NZD 111, respectively, to prevent an exacerbation and a severe exacerbation. From a societal perspective it is cost-saving NZD 70 (95% CI 2–134). Findings were robust to scenario analyses.

Conclusion For patients with mild asthma, as-needed budesonide-formoterol 200/6 µg is cost-saving from health-system, patient and societal perspectives, while improving outcomes, dominating maintenance budesonide plus as-needed salbutamol. Compared with as-needed salbutamol, as-needed budesonide-formoterol is cost-effective from a health-system perspective and dominates from a societal perspective.

Introduction

The Global Initiative for Asthma (GINA) recommends anti-inflammatory reliever therapy using a combination inhaled corticosteroid (ICS)-formoterol reliever alone for mild asthma at steps 1–2 [1, 2]. This

titrates the ICS dose to the frequency of symptoms and reduces the risk of severe exacerbations, with a lower mean ICS dose and systemic corticosteroid burden, compared with maintenance ICS plus short-acting β_2-agonist (SABA) reliever [3–5]. This approach is also simpler to use without the need for two inhalers or regular daily treatment and it is preferred by most patients [6]. Compared with SABA alone, a combination ICS-formoterol reliever markedly reduces severe exacerbations, emergency-department visits and hospitalisations [4, 5].

However, budesonide-formoterol combination inhalers currently cost more than either SABA or ICS inhalers. This could limit patient access and increase health-system costs. Existing cost-effectiveness analyses of as-needed budesonide-formoterol have all been based on the double-blind SYGMA 1 and/or 2 studies [7–10], which have limited external validity to real-world clinical practice.

We report a prespecified within-trial economic evaluation of the open-label, three-arm Novel START study comparing the cost-effectiveness of as-needed budesonide-formoterol for preventing exacerbations in patients with mild asthma *versus* maintenance budesonide with as-needed salbutamol, and *versus* as-required salbutamol monotherapy.

Methods

Study participants and interventions

Novel START was a 52-week, open-label, parallel-group, randomised controlled trial conducted between 2016 and 2018, in New Zealand (NZ), UK, Italy and Australia (Australian New Zealand Clinical Trials Registry, number ACTRN12615000999538). Adults with a self-reported doctor diagnosis of asthma were eligible if they had been using a SABA between twice a month and twice a day as their sole asthma therapy for the previous 3 months. For those reporting a severe exacerbation in the past year (7.3%), there was no minimum requirement for SABA use. Key exclusion criteria were asthma hospitalisation in the previous year and a smoking history of >20 pack-years (9.6% were current smokers at enrolment). Randomised participants (n=668, 55% female) had a mean age of 36 years (range 18–75).

Randomisation was to one of three groups: salbutamol 100 µg (Ventolin; GlaxoSmithKline), two inhalations as needed for symptom relief (n=223, of which 184 were in NZ); maintenance budesonide 200 µg (Pulmicort Turbuhaler; AstraZeneca) one inhalation twice daily plus salbutamol 100 µg (Ventolin), two inhalations as needed for symptom relief (n=225, NZ 185); and budesonide-formoterol 200/6 µg (Symbicort Turbuhaler; AstraZeneca), one inhalation as needed for symptom relief (n=220, NZ 182). Seven trial visits occurred over the course of the 52-week follow-up period, at weeks 0 (randomisation), 6, 12, 22, 32, 42 and 52. The protocol and outcomes are published elsewhere [11, 12].

Clinical outcomes

Exacerbations were defined as worsening asthma leading to either an urgent medical care consultation (primary care, emergency department or hospital admission), a prescription of systemic corticosteroids, or an episode of high β_2-agonist use (>16 actuations of salbutamol or more than eight actuations of budesonide-formoterol within a 24-hour period).

Severe exacerbations were defined as worsening asthma resulting in a prescription of systemic corticosteroids for ⩾3 days, or hospitalisation or emergency-department visit requiring systemic corticosteroids [13]. Patients were withdrawn if they experienced either one severe exacerbation, three non-severe exacerbations separated by ⩾7 days, or unstable asthma resulting in a change in randomised treatment for >2 weeks.

As previously reported in the trial outcomes paper [12], the annualised exacerbation rate in the budesonide-formoterol group was lower than in the salbutamol group (absolute rate 0.195 *versus* 0.400, relative rate 0.49, 95% CI 0.33–0.72) and did not differ significantly from the maintenance budesonide group (absolute rate 0.195 *versus* 0.175, relative rate 1.12, 95% CI 0.70–1.79). The number of severe exacerbations was lower in the budesonide-formoterol group than in both the salbutamol (9 *versus* 23, relative risk 0.40, 95% CI 0.18–0.86) and maintenance budesonide groups (9 *versus* 21, relative risk 0.44, 95% CI 0.20–0.96).

Economic analysis

The analytic time horizon was the 12-month follow-up period of the trial. The primary perspective adopted was the health-system perspective (including healthcare costs to the patient), with the societal perspective (health-system plus time-off-work costs) as secondary. Only participants recruited in NZ, who comprised the majority of the trial's participants (NZ 82%, n=551 out of 668) were included in the analysis. For participants who withdrew from the study, it was assumed that they would have been treated with current

standard-of-care treatment using maintenance budesonide plus as-needed SABA for the remainder of the 12-month follow-up period. Those randomised to maintenance budesonide and withdrawn due to poor control were assumed to have been stepped up to maintenance budesonide-formoterol plus as-needed SABA.

Electronic inhaler monitors (Adherium Ltd), which recorded the date and time of inhaler actuations, were incorporated in all inhalers dispensed in the study. Participants were given a log for recording urgent medical visits and the dose and dates of all prescribed and over-the-counter pharmaceuticals used. The analysis was conducted on an intention-to-treat basis, with the base case using 30 separate datasets (based on the fraction of missing data) generated by multiple imputation by chained equations to account for missing inhaler actuation data on withdrawal or loss to follow-up [14].

Medication use was valued by actuations used and tablets taken by each participant, using the NZ Pharmaceutical Schedule (April 2025) [15], including relevant dispensing fees, pharmacy margins and patient charges. These were costed by W.L. with assistance from T. Hung; R.J.H. and R.B. adjudicated whether these were exacerbation-related costs and therefore included in the analysis. Most prescription medicines are fully subsidised by the NZ government, so patients are not required to pay any additional surcharge. However, a standard NZD 5 prescription charge (patient co-payment) per item dispensed is normally required unless certain conditions, described below, are met. Costs for general-practitioner (GP) appointments, emergency-department visits and hospitalisations were taken from the NZ Pharmaceutical Management Agency [16]. Days off work were valued using the median daily wage from Stats NZ [17]. Costs were reported in 2025 NZD exclusive of Goods and Services Tax, adjusted *via* the consumers price index where necessary.

Seemingly unrelated regression was used to control for between-group differences in prognostic variables at baseline (number of severe exacerbations in the previous 12 months and SABA use in the previous 4 weeks) with 1000 replications of bias-corrected and accelerated bootstrapping to evaluate the uncertainty around the estimates of cost and effect [18]. For the 30 multiple imputation datasets, Rubin's [19] rules were applied to combine the 30 seemingly unrelated regression estimates and their 95% confidence intervals to obtain the final pooled seemingly unrelated regression estimates and 95% confidence intervals. W.L. conducted the analyses with assistance from T. Hung and I.P. The incremental cost-effectiveness ratios, that is, the costs per asthma exacerbation or severe asthma exacerbation averted from using as-needed budesonide-formoterol compared with maintenance budesonide and salbutamol monotherapy, are reported when the intervention is both more costly and more effective than the comparator [20]. Cost-effectiveness acceptability curves were generated to show the probability that the intervention is cost-effective for a range of willingness-to-pay thresholds to avert an asthma exacerbation.

In the base-case analysis, all patients pay the full prescription charge (NZD 5 including Goods and Services Tax) [16]. One scenario exempted all participants from the prescription charge, as would be the case if: 1) the family unit received ⩾20 new subsidised prescription-medicine items, for any conditions, per year; or 2) universal prescription-charge exemptions continued, which ended in NZ in July 2024. Another scenario assessed the impact of substituting the branded study inhalers with cheaper generics, where available (in NZ this is limited to salbutamol). Ventolin was substituted with a generic salbutamol 100 µg inhaler, which would avoid a patient surcharge.

Stata/SE v18.0 was used for all modelling and analyses. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 Statement [21] guided this report.

Results

Table 1 details the baseline characteristics of the 551 NZ participants. Full clinical findings have been reported elsewhere [12]. Table 2 shows the resource use, costs and exacerbations for the NZ participants in the trial. There were no asthma-related inpatient hospitalisations in any group. GP visits for medical review, number of patients requiring oral corticosteroids and days off work were lowest in the as-needed budesonide-formoterol group. The budesonide-formoterol group had similar inhaler costs to the maintenance budesonide group but lower exacerbation-related healthcare costs (GP medical review and emergency-department visits) and fewer days off work due to asthma, resulting in lower healthcare and societal costs than maintenance budesonide. Correspondingly, the budesonide-formoterol group has lower estimated mean out-of-pocket costs than the maintenance budesonide group (supplementary table S1).

In all scenarios (table 3), as-needed budesonide-formoterol therapy was both less costly and more effective in reducing severe exacerbations than maintenance budesonide; hence incremental cost-effectiveness ratios are irrelevant. Mean cost savings ranged from NZD 8.83 to 26.20 per patient over 12 months. If the health

TABLE 1 Baseline characteristics of the New Zealand participants (n=551) in the Novel START clinical trial

Characteristics	BUD-FOR (n=182)	MAIN BUD (n=185)	SALB (n=184)
Age, years	35.0±13.8	33.6±13.8	33.9±13.6
Female sex	105 (57.7)	108 (58.4)	93 (50.5)
Asthma Control Questionnaire–5 score	1.1±0.7	1.1±0.7	1.1±0.7
Patient-reported short-acting β_2-agonist use in the 4 weeks before enrolment, number of occasions per week	3.7±3.4	3.1±2.9	3.3±3.4
Hospital admissions for asthma at any time before enrolment, per patient	0.3±1.4	0.3±1.0	0.3±1.0
Severe exacerbations in the previous 12 months	10 (5.5)	15 (8.1)	18 (9.8)

Data are presented as mean±SD or n (%) of patients. BUD-FOR: as-needed budesonide-formoterol; MAIN BUD: maintenance budesonide; SALB: as-needed salbutamol.

system is willing to pay ⩾NZD 10 to avert a severe exacerbation, regardless of the scenario, the probability that as-needed budesonide-formoterol is cost-effective, compared with maintenance budesonide, is >90% (figure 1). If the health system is willing to pay ⩾NZD 240, this probability increases to ⩾95% (again regardless of the scenario). When a societal perspective was considered, cost savings were higher because patients using budesonide-formoterol had fewer mean days off work due to exacerbations, 0.1, *versus* maintenance budesonide, 0.15.

TABLE 2 Resource use, costs (2025 NZD) and exacerbations during 12-month follow-up in the New Zealand participants (n=551), by treatment arm

	Resource use and exacerbations			Costs, NZD			
	BUD-FOR (n=182)	MAIN BUD (n=185)	SALB (n=184)	Unit costs[#]	BUD-FOR	MAIN BUD	SALB
Inhaler-related use							
Inhaler actuations per patient over 12 months[¶]							
Budesonide-formoterol 200/6 µg	161.5	16.4*	0	0.300	48.46	4.91	0.00
Budesonide 200 µg	61.8	435.7*	89.7	0.104	6.43	45.31	9.33
Salbutamol 100 µg	25.2	143.2*	304.3*	0.028	0.71	4.01	8.52
Ventolin surcharge				0.026	0.66	3.72	7.91
Subtotal (for inhalers)					56.25	57.96	25.76
Index GP visit	1	1	1	98.88	98.88	98.88	98.88
Repeat Rx for trial inhalers (total)	0.18 (34)	0.28* (51)	0.18 (34)	18.54	3.43	5.11	3.40
Less patient Rx charges for inhalers				4.35	7.61	11.50	6.61
Exacerbation-related use							
GP visits for medical review (total)	0.06 (11)	0.11 (20)	0.16* (30)	98.88	5.98	10.69	16.12
Emergency room visits (total)	0 (0)	0.02 (3)	0.02 (4)	457.34	0	7.42	9.94
Oral steroids with or without antibiotics, patients	9	16	19		0.25	0.24	0.72
Less patient Rx charges				4.35	0.36	0.45	0.73
Mean healthcare costs[+]					**156.81**	**168.34**	**147.48**
Days off work due to asthma (total)	0.10 (19)	0.15 (28)	0.38* (70)	268.60	28.04	40.65	102.18
Mean societal costs					**184.86**	**208.99**	**249.67**
Estimated mean patient out-of-pocket costs[§]					74.15	86.90	87.58
Exacerbations (per patient over 12 months)							
Severe exacerbations (total)	0.04 (8)	0.09 (17)	0.11 (20)				
All exacerbations (total)	0.16 (30)	0.15 (28)	0.35 (65)				

Numbers are averaged over all randomised patients in an arm, except the numbers in brackets under "Resource use and exacerbations", which are totals for each treatment arm. Purchasing power parity 2025 NZD 1=EUR 0.44=GBP 0.45. Subtotal inhaler costs and mean healthcare and societal costs are highlighted in bold font. BUD-FOR: as-needed budesonide-formoterol; MAIN BUD: maintenance budesonide; SALB: as-needed salbutamol; GP: general practitioner; Rx: prescription. [#]: cost per actuation; [¶]: multiple imputation used for missing inhaler actuation data; [+]: sum of the above less patient Rx charges; [§]: includes Ventolin brand surcharge, 50% of GP visit fees, repeat Rx fees and 15% Goods and Services Tax; *p<0.05 for difference (in resource use) between the budesonide-formoterol arm, Poisson or negative binomial regression for count data, chi-square or Fisher's exact test for categorical data, not controlled for multiplicity.

TABLE 3 Cost analyses of as-needed budesonide-formoterol (n=182) *versus* maintenance budesonide (n=185)

Scenarios	Healthcare costs, NZD (95% CI)	Societal costs, NZD (95% CI)
Base case		
BUD-FOR	156.83 (145–172)	184.87 (153–251)
MAIN BUD	168.35 (151–199)	209.00 (167–270)
Adjusted cost difference[#]	−12.09 (−28–0)	−22.20 (−58–15)
No prescription charge		
BUD-FOR	164.79 (152, 180)	192.83 (160–259)
MAIN BUD	180.29 (163, 212)	220.94 (180–282)
Adjusted cost difference[#]	−16.09 (−33– −3)	−26.20 (−62–12)
Generic salbutamol[¶]		
BUD-FOR	156.17 (144–171)	184.21 (152–250)
MAIN BUD	164.63 (148–195)	205.28 (165–265)
Adjusted cost difference[#]	−8.83 (−25–4)	−18.94 (−54–18)

Purchasing power parity 2025 NZD 1=EUR 0.44=GBP 0.45. Societal costs: healthcare costs plus costs of exacerbation-related days off work; BUD-FOR: as-needed budesonide-formoterol; MAIN BUD: maintenance budesonide; [#]: estimated using seemingly unrelated regression controlling for baseline number of severe exacerbations and baseline short-acting β_2-agonist use; [¶]: substitution of Ventolin with generic salbutamol.

Changing from as-needed salbutamol to as-needed budesonide-formoterol can be achieved at an incremental cost to the health system of NZD 38 per exacerbation averted or NZD 111 per severe exacerbation averted (table 4) and is likely cost-effective (figures 2 and 3). When days off work due to exacerbations are included in a societal perspective, a change to as-needed budesonide-formoterol is cost-saving due to higher mean days off, 0.38, in the as-needed salbutamol arm (figure 4). The complete-case analysis (n=381) of the NZ participants who were not withdrawn from the study or lost to follow-up is shown in supplementary table S2.

Discussion

This within-trial cost-effectiveness analysis using individual patient-level data from one of the landmark studies of as-needed budesonide-formoterol for mild asthma [12, 22–24] demonstrates that as-needed budesonide-formoterol, compared with maintenance budesonide, for mild asthma probably results in annual cost-savings to the health system of NZD 12 (95% CI 0–28) per patient, rising to NZD 16 (95% CI 3–33) when there is no prescription charge payable by the patient.

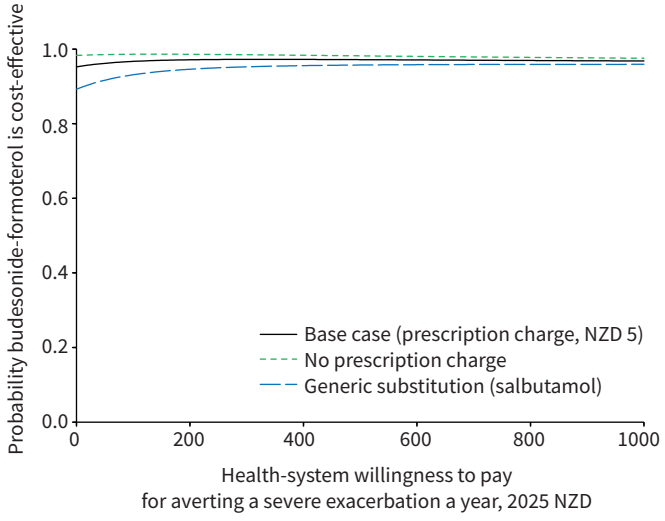

FIGURE 1 Cost-effectiveness acceptability curves (averting a severe exacerbation from a health-system perspective) for as-needed budesonide-formoterol *versus* maintenance budesonide, controlling for severe exacerbations in the previous 12 months and baseline short-acting β_2-agonist use. Note that in New Zealand, generics are available only for salbutamol.

TABLE 4 Cost(-effectiveness) of as-needed budesonide-formoterol (n=182) *versus* as-needed salbutamol (n=184)

Scenarios	Healthcare costs (NZD), 95% CI	Societal costs (NZD), 95% CI
Base case		
BUD-FOR	156.83 (145–172)	184.87 (153–251)
SALB	147.48 (128–179)	249.67 (169–368)
Adjusted cost difference[#]	7.22 (−10–22)	−70.09 (−134– −2)
$ICER^{\#}_{exacerbation}$	38	Dominant
$ICER^{\#}_{severe\ exacerbation}$	111	Dominant
No prescription charge		
BUD-FOR	164.79 (152–180)	192.83 (160–259)
SALB	154.83 (134–186)	257.02 (175–377)
Adjusted cost difference[#]	7.73 (−10–23)	−69.58 (−133– −1)
$ICER^{\#}_{exacerbation}$	41	Dominant
$ICER^{\#}_{severe\ exacerbation}$	119	Dominant
Generic salbutamol[¶]		
BUD-FOR	156.17 (144–171)	184.21 (152–250)
SALB	139.57 (121–169)	241.76 (160–361)
Adjusted cost difference[#]	14.69 (−2–29)	−62.62 (−127–5)
$ICER^{\#}_{exacerbation}$	77	Dominant
$ICER^{\#}_{severe\ exacerbation}$	225	Dominant

Purchasing power parity 2025 NZD 1=EUR 0.44=GBP 0.45. Societal costs: healthcare costs plus costs of exacerbation-related days off work; BUD-FOR: as-needed budesonide-formoterol; ICER: incremental cost-effectiveness ratio, the cost per (severe) exacerbation prevented is only reported when as-needed budesonide-formoterol is more costly and more effective (it prevents 0.06 more severe exacerbations and 0.18 exacerbations); SALB: as-needed salbutamol; dominant: when as-needed budesonide-formoterol is both less costly and more effective; [#]: estimated using seemingly unrelated regression controlling for baseline number of severe exacerbations and baseline short-acting β_2-agonist use; [¶]: substitution of Ventolin.

The latter scenario reflects the position in NZ from July 2023 to June 2024, when the Labour government abolished the NZD 5 prescription charge on equity grounds. Similar compelling arguments for prescription-charge exemption have previously been made for patients with asthma in England; there are no prescription charges in Scotland, Wales or Northern Ireland [25]. One consequence of dropping the prescription charge is the loss of this government revenue, which is used to subsidise costs elsewhere in

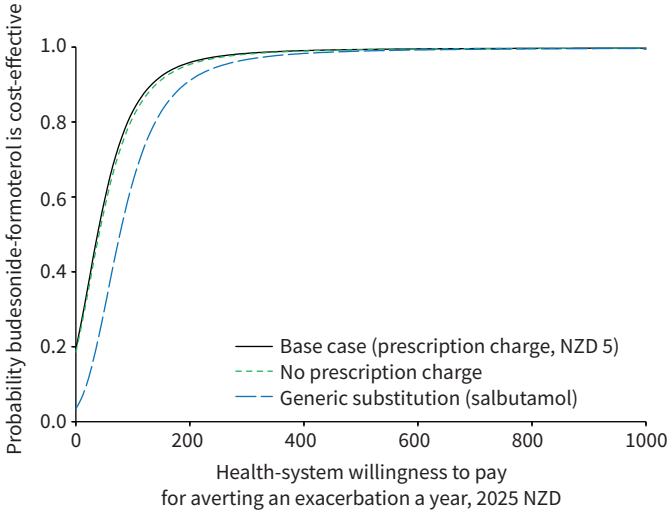

FIGURE 2 Cost-effectiveness acceptability curves (averting an exacerbation from a health-system perspective) for as-needed budesonide-formoterol *versus* as-needed salbutamol, controlling for severe exacerbations in the previous 12 months and baseline short-acting β_2-agonist use. Note that in New Zealand, generics are available only for salbutamol.

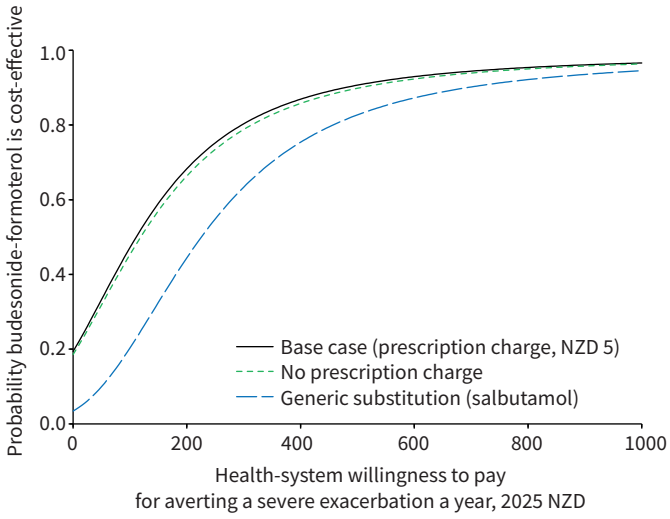

FIGURE 3 Cost-effectiveness acceptability curves (averting a severe exacerbation from a health-system perspective) for as-needed budesonide-formoterol *versus* as-needed salbutamol, controlling for severe exacerbations in the previous 12 months and baseline short-acting β_2-agonist use. Note that in New Zealand, generics are available only for salbutamol.

the health system. In our "no prescription charge" scenario, costs in the maintenance budesonide arm would increase more than in the as-needed budesonide-formoterol arm (table 3) because the health system loses more of the offsetting prescription-charge income from patients on maintenance budesonide (due to the need for separate reliever and preventer inhalers) than from patients on as-needed budesonide-formoterol with a combined inhaler. This has the seemingly paradoxical effect of increasing annual cost savings per patient from NZD 12 to 16.

Patients on budesonide-formoterol had fewer exacerbation-related days off work than patients on maintenance budesonide, leading to further societal cost savings. As-needed budesonide-formoterol, where fewer inhalers need to be dispensed and severe exacerbations are less frequent, might also cut the

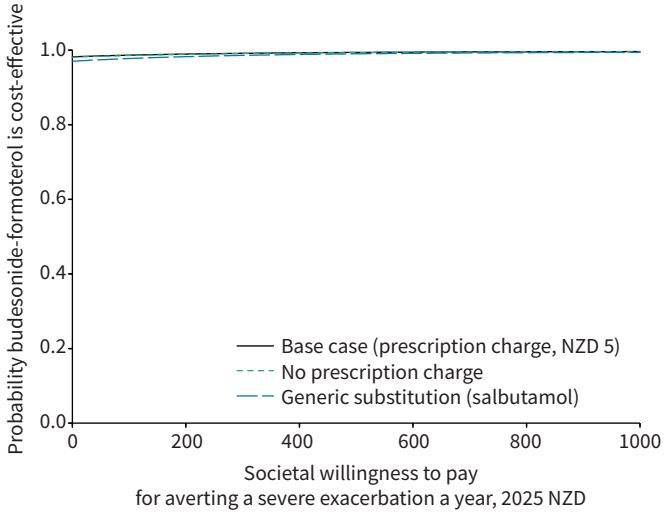

FIGURE 4 Cost-effectiveness acceptability curves (averting a severe exacerbation from a societal perspective) for as-needed budesonide-formoterol *versus* as-needed salbutamol, controlling for severe exacerbations in the previous 12 months and baseline short-acting β_2-agonist use. Note that in New Zealand, generics are available only for salbutamol.

out-of-pocket burden to patients by reducing the number of prescription items required (supplementary table S1).

Compared with as-needed salbutamol alone, as-needed budesonide-formoterol would cost the health system NZD 38 and NZD 111, respectively, to prevent an exacerbation and a severe exacerbation. However, when the savings due to fewer exacerbation-related days off work are considered, as-needed budesonide-formoterol is cost-saving from a societal perspective. Our NZD 111 (2025 value) estimate per severe exacerbation avoided is lower than the EUR 267 (2003 value) reported elsewhere [26]. These costs compare favourably to a recent study that assumed patients with moderate–severe asthma were willing to pay up to AUD 2651 to avoid an exacerbation [27].

In this study, only 8% of participants experienced a severe exacerbation and none required inpatient admission; exacerbations were managed in the community with inexpensive treatments, such as prednisone. Thus, mean cost estimates in this study are highly dependent on inhaler costs; hence, multiple imputation by chained equations, rather than mean imputation, was used to estimate missing inhaler actuation data on withdrawal and loss to follow-up.

Four previous cost-effectiveness analyses of as-needed budesonide-formoterol in patients with mild asthma have been based on the SYGMA 1 and/or 2 studies, using Markov or decision tree models [7–10]. These studies were double-blind, placebo-controlled trials of as-needed budesonide-formoterol in mild asthma [22, 23]. On the basis of clinical efficacy data for 1 year, Fitzgerald *et al.* [7] found that as-needed budesonide-formoterol was associated with projected lifetime discounted cost-savings of GBP 293 (95% CI −123–697) per UK patient with mild asthma compared with maintenance beclometasone plus as-needed terbutaline, a result that was not statistically significant. This approximates to a GBP 13 cost saving each year over 40 years (at their 3.5% discount rate). Cost differences with our NZ "no prescription charge" scenario, which showed a lower yet statistically significant cost saving of NZD 16 (95% CI 3–33), might be mainly attributable to the typically lower pharmaceutical costs in the NZ health system relative to other high-income countries [28]. Besides the fact that Fitzgerald *et al.*'s study was a lifetime decision-analytic model set in the UK, whereas ours is a within-trial analysis set in NZ, there are a number of other methodological differences. As noted, their data were from a placebo-controlled trial in patients needing daily ICS treatment by GINA 2012 criteria, whereas Novel START also included patients with less-frequent symptoms and was an open-label trial that investigated the way that patients would use as-needed ICS-formoterol in real life (albeit with frequent study visits). Furthermore, our study also considered patient charges, costs of non-severe and severe exacerbations, costing of both branded and generic trial inhalers, another comparator (salbutamol monotherapy) and a societal perspective.

Sadatsafavi *et al.* [8] and Buendía and Patiño [10] estimated that as-needed budesonide-formoterol could result in incremental cost savings over maintenance ICS in Canada and Colombia, respectively. In a Malaysian context, Gopal *et al.* [9] estimated an incremental cost-effectiveness ratio of MYR 696 per severe exacerbation avoided with budesonide-formoterol compared with regular ICS. They also estimated that switching from salbutamol monotherapy to as-needed budesonide-formoterol would lead to annual cost savings to the Malaysian Ministry of Health. However, the 95% confidence intervals for costs in the budesonide-formoterol cohort (MYR 384–1333) and the salbutamol cohort (MYR 465–1527) were similar and overlapping. This contrasts with our findings in NZ, where budesonide-formoterol was costlier to the health system than salbutamol alone; however, from a societal perspective, the cost saving was statistically significant (table 4). Although salbutamol monotherapy for asthma treatment is no longer recommended by international guidelines, its use is likely to remain widespread, particularly in low- and middle-income countries [1, 29].

A strength of the Novel START trial is that the actuations of each inhaler were recorded electronically, providing accurate estimates of the overall cost based on the number of doses used. The study was designed to approximate normal use of these inhalers, without double-blinding or placebo inhalers. However, the number of doses used in the study will not reflect the real-world costs attributable to lost inhalers, early replacement before depletion and having multiple inhalers (*e.g.* at work and home). These factors particularly underestimate the costs for maintenance budesonide due to the need for separate reliever and preventer inhalers. Conversely, adherence to regular ICS is likely to be lower in clinical practice and we may have overestimated the actual cost of regular budesonide treatment. However, lower adherence to regular budesonide would also be expected to lead to a higher risk for exacerbations and more healthcare use.

Although the Novel START trial recruited participants from four countries, 82% of them came from one country, NZ, with the remaining 18% coming from the other three countries (England, Australia and Italy).

The economic analysis focused solely on the NZ participants. Inclusion of the small number of the other countries' participants (which had between seven and 18 participants per treatment arm) would complicate the analysis and require assumptions around access to care; for example, assuming that access to GP services is the same in NZ as in England regardless of cost, which may not hold true.

To enhance external validity to other high-income countries, we adopted health-system and societal perspectives and tested the impact of universal prescription charge exemption and generic substitution. Still, our findings may not be generalisable to countries where health-system funding and costs differ substantively; however, the reported healthcare utilisation should be informative.

Cost-effectiveness analysis was prespecified in this study [11], but some methods were modified *post hoc* in response to reviewer suggestions, and not all healthcare resource utilisation data were collected. Those who withdrew from the study because of recurrent or severe exacerbations or treatment failure were started on regular ICS and SABA treatment because this was the standard step 2 treatment at the time. For treatment failure in the maintenance budesonide group, we assumed that patients would be stepped up to maintenance budesonide-formoterol. As more patients in the maintenance budesonide and salbutamol monotherapy groups withdrew due to severe exacerbations, it is likely that the actual healthcare costs and exacerbation-related days off work in these groups were higher compared with the budesonide-formoterol group, further underestimating the potential cost savings or cost-effectiveness of budesonide-formoterol.

Conclusion

Changing patients from traditional regular ICS with as-required SABA therapy to a regimen with budesonide-formoterol only as needed is cost-saving to the patient, health system and to society, in addition to improving health outcomes. Switching from salbutamol monotherapy may come at a modest cost to the health system but is cost-saving if one considers the reduction in exacerbation-related days off work.

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