

Budget impact analysis of inhaled corticosteroid plus formoterol fixed-dose combination for symptom relief and maintenance therapy in chronic asthma management

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CONFLICT OF INTEREST DETAILS

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- HE²RO shared unpublished data on hospital costs during the COVID-19 pandemic.

KEY FINDINGS

- We conducted a budget impact analysis to compare standard of care treatment to an inhaled corticosteroid (ICS)/formoterol combination inhaler for symptom relief in adults and adolescents aged ≥ 12 years with intermittent asthma (symptoms less than twice per month) and mild persistent asthma (symptoms ≥ 2 times per month, but < 4 -5 days per week); and ICS/formoterol as maintenance-and-reliever therapy (MART) for those with moderate asthma (symptoms almost daily or waking due to asthma $\geq$ once a week), within the South African public sector, assuming current asthma prevalence and treatment coverage ('status quo').
- We estimated that implementing ICS/formoterol combination inhaler therapy would reduce pharmaceutical costs by R937,613 per annum. Estimated overall pharmaceutical cost for the current standard of care across all asthma severities was R202.76 million, compared to R201.82 million for the ICS/formoterol strategy.
 - Pharmaceutical costs were higher for ICS/formoterol than the standard of care for moderate asthma only.
- We estimated that implementing ICS/formoterol would increase total healthcare costs (pharmaceutical and non-pharmaceutical) by R31.9 million per annum. Estimated total healthcare cost for the standard of care in the status quo scenario was R471.1 million, compared to R502.96 million for the ICS/formoterol strategy
 - For mild intermittent asthma, ICS/formoterol increases total costs, largely driven by our assumption of three visits per year to a healthcare facility for ICS/formoterol, compared to two visits per year for standard of care.
 - For mild persistent asthma, ICS/formoterol reduces both pharmaceutical and healthcare utilisation costs, resulting in net savings.
 - For moderate asthma, pharmaceutical costs are higher for ICS/formoterol, but these are offset by lower healthcare utilisation, leading to a net saving.
- A rapid transition to the ICS/formoterol from current standard of care (20% uptake per year) appears more cost-efficient from a pharmaceutical budget perspective. By Year 5, the total pharmaceutical net cost saving across all asthma severities amounts to R988,498. In contrast, slow adoption (10% uptake per year) leads to total pharmaceutical net cost saving across all asthma severities of R494,249.

Policy and practical implications

- The findings support policy shifts towards ICS/formoterol therapy to improve asthma outcomes and reduce pharmaceutical costs.
- The proposed strategy could optimise resource allocation in the national health budget for the public sector.
- Improving local epidemiological data through a national asthma registry and strengthening health information systems are essential to achieve efficient and equitable evidence-informed decision-making.

EXECUTIVE SUMMARY

Medicine (Intervention): Inhaled corticosteroid/formoterol

Medicine (ATC): R03AK07 (formoterol and budesonide), R03AK08 (formoterol and mometasone) R03AK11 (formoterol and fluticasone).

Note that this BIA focuses on the ICS budesonide in combination with formoterol. Other ICS/formoterol options are included in the therapeutic interchange database.

Indication: Intermittent mild asthma, persistent mild asthma, moderate asthma (J45.0-1/J45.8-9)

Research questions:

PICO 1: Among adults and adolescents ≥ 12 years with mild intermittent asthma (symptoms $<$ twice per month), is inhaled ICS/formoterol affordable compared to inhaled short-acting beta2 agonist (SABA) combined with inhaled corticosteroid (ICS) administered as needed for symptom relief?

PICO 2: Among adults and adolescents ≥ 12 years with mild persistent asthma (symptoms $\geq$ twice a month), is inhaled ICS/formoterol taken as reliever therapy affordable, compared with daily low-dose ICS and a SABA as needed for symptom relief?

PICO 3: Among adults and adolescent ≥ 12 years with moderate asthma (symptoms almost daily or waking due to asthma $\geq$ once a week), is inhaled ICS/formoterol taken daily and as reliever therapy, affordable compared to daily long-acting beta2 agonist (LABA)/ ICS controller and a SABA as needed for symptom relief?

Patient population: Adolescents (≥ 12 years) and adults with asthma

Level of Care: Primary Healthcare and adult hospital level

Prescriber level: Nurse prescriber (mild asthma)/ Medical officer initiated (moderate asthma)

Current Standard of Care/ Comparator(s) per PICO:

PICO 1: SABA inhaler plus ICS inhaler administered as needed for symptom relief

PICO 2: Daily low-dose ICS inhaler and as-needed SABA inhaler

PICO 3: Daily combination ICS/LABA inhaler and as-needed SABA inhaler

Intervention(s) per PICO:

PICO 1: ICS/formoterol as needed for symptom relief

PICO 2: ICS/formoterol as needed for symptom relief

PICO 3: ICS/formoterol as maintenance and as-needed reliever therapy (MART)

Outcomes

Pharmaceutical and healthcare costs

Background

Asthma burden in South Africa is significant with 331.3 DALYs per 100,000 and a mortality rate of 9.09 per 100,000.

The current standard of care for symptom relief amongst adolescents/adults with mild intermittent and mild persistent asthma in the South African public sector is an as-needed inhaled corticosteroid (ICS) and a SABA (administered as separate inhalers). The NEMLC conducted evidence reviews, to evaluate the efficacy and safety of ICS/formoterol (a long acting β_2 -agonist, LABA) combination therapy compared to ICS plus SABA (standard of care) for symptom relief in mild intermittent (PICO 1) and mild persistent (PICO 2) asthma, and ICS/formoterol for symptom relief and maintenance therapy (maintenance-and-reliever therapy, MART) for moderate (PICO 3) asthma. Randomised clinical trial evidence demonstrated that for mild persistent asthma, as-needed ICS/formoterol likely results in little to no difference in acute severe exacerbations requiring systemic corticosteroids, asthma-related hospital admissions, mortality, adverse events (AEs) and serious adverse events (SAEs), but a slight reduction in asthma-related emergency room visits compared to standard of care (moderate

to high certainty evidence). Amongst adults/adolescents with moderate asthma, compared to standard of care, ICS/formoterol as MART showed a reduction in severe asthma exacerbations, systemic corticosteroid use, asthma-related emergency room visits or hospitalisations, with little to no difference in mortality, SAEs and AEs (moderate to high certainty evidence). There is a paucity of evidence directly comparing as-needed ICS/SABA to ICS/formoterol for mild intermittent asthma; however, expert opinion suggests comparable efficacy and safety.

We conducted a pharmacoeconomic analysis to determine the budget impact of implementing the ICS/formoterol strategy for adolescents/adults with asthma in the South African public healthcare sector.

Methods

We built budget impact, decision-analytic models using 12-month scenarios comparing costs of current standard treatment guidelines ('standard of care') with the implementation of an ICS/formoterol strategy in adults and adolescents aged 12 and over with asthma in South Africa, assuming current asthma prevalence and treatment coverage ('status quo') (see Section II Budget analysis: Models). The status quo was determined using national procurement data, which was triangulated with estimates from public sector tenders, dispensing data from the Western Cape public sector, and data from the Central Chronic Medicine Dispensing and Distribution (CCMDD) program.

Due to limited local prevalence data, available data were supplemented with utilisation data and expert opinion. The rates of exacerbations, adverse effects, and use of reliever therapy were sourced from randomised controlled trial data in the rapid evidence syntheses. In the absence of direct comparison evidence, we used a conservative estimate of similar efficacy of ICS/formoterol and standard of care for mild intermittent asthma. Direct medical costs, including the costs of asthma medications and treating exacerbations, were obtained from public sector pharmaceutical tenders and the NDoH Uniform Patient Fee Schedule, and hospitalisation costs were extrapolated from data collected by HE2RO during the COVID-19 pandemic. Population data were obtained from StatsSA. Assumptions regarding the number of inhalers needed for mild intermittent asthma, severe asthma prevalence in adults, referrals from primary healthcare (PHC), ICU and general ward admission rates, and length of stay were based on a combination of expert opinion and published studies (see Sensitivity analyses section and Table 14). We conducted scenario analyses from a payer perspective and deterministic sensitivity analyses. An ethics waiver was obtained from the SAMRC Human Research Ethics Committee for the collection of delinked anonymised secondary data from the Western Cape Department of Health and aggregated utilisation data from the NDoH.

Rapid vs slow uptake rate: Besides the status quo scenario, we modelled slow (10%) and rapid (20%) uptake scenarios, within the current budget, factoring in an annual population growth of 1.3%.

Results

We estimated a target population of 10.958 million uninsured adolescents/adults with asthma, based on local epidemiological data, public-sector utilisation data, and expert opinion. South Africa's public-sector coverage was estimated to be 606,000 (6%) overall, with approximately 46% with mild intermittent, 46% mild persistent, and 8% moderate to severe asthma (see Table 8). In PICO 1, pharmaceutical costs decreased from R51.15 million in the standard of care scenario to R49.78 million in the ICS/formoterol scenario, reflecting a reduction of R1.37 million. However, non-pharmaceutical costs increased by R63.89 million, leading to a higher total cost for ICS/formoterol. In PICO 2, pharmaceutical costs decreased from R110.71 million for standard of care to R99.91 million for ICS/formoterol, a reduction of R10.81 million. Additionally, non-pharmaceutical costs declined by R10.36 million, resulting in an overall cost saving of R21.16 million. This scenario presents the most substantial cost reduction among the three asthma severity groups. In PICO 3, pharmaceutical costs increased from R40.89 million in the standard of care to R52.13 million with ICS/formoterol, an increase of R11.24 million. However, non-pharmaceutical costs decreased by R20.73 million, leading to an overall total cost saving of R9.49 million. Estimated total healthcare costs (pharmaceutical and non-pharmaceutical) for the standard of care scenario is R471.1 million, compared to R502.96 million for the ICS/formoterol strategy (an increase of R31.9 million).

The increase in total healthcare costs is largely driven by our estimate of three visits per year to a healthcare facility for medication supply for ICS/formoterol (60-dose inhaler), for adults/adolescents with mild intermittent asthma compared to two visits for standard of care (SABA and ICS: 200-dose inhalers each). The overall national health budget for 2024 was R62.2 billion.

A rapid transition to the ICS/formoterol strategy appears more cost-efficient from a pharmaceutical budget perspective, yielding overall savings compared to maintaining the current standard of care. By year 5, the total pharmaceutical net cost saving amounts to R988,498. In contrast, slow adoption leads to total pharmaceutical net cost savings of R494,249. Sensitivity analysis indicates uncertainty surrounding the costs of emergency room visits, hospitalisations and ICU admissions, and the proportion of people with asthma referred from PHC for hospitalisation. This introduces uncertainty around the total budget impact but does not change the overall conclusion of likely cost savings with ICS/formoterol. Significant uncertainty remains around the effectiveness of SABA with ICS in comparison to ICS/formoterol in mild intermittent asthma. There is further uncertainty regarding the utilisation patterns of inhalers for the standard of care, which could contribute to higher treatment costs in the standard of care arm. Furthermore, there is high uncertainty around the proportion of adults with severe asthma, which significantly impacts the total budget impact for managing asthma.

Conclusion

The budget impact analysis indicates that adopting ICS/formoterol therapy for asthma in adults and children ≥ 12 years could generate cost savings for the South African public health sector for the currently treated population. Reduced healthcare utilisation costs (particularly fewer hospitalisations and emergency visits) with ICS/formoterol compared to standard of care offset pharmaceutical costs in most scenarios, leading to net savings. Successful implementation will require investment in procurement, provider training, and patient education to ensure adherence. Given data limitations, further research is needed to refine cost estimates. Price monitoring and negotiations could enhance affordability and expand access, thus supporting sustainable asthma management and efficient resource allocation.

Introduction

Current evidence favours maintenance and reliever therapy (MART) with inhaled corticosteroid (ICS)/formoterol over South Africa's current standard of care for asthma. NEMLC recommended that a budget impact analysis of ICS/formoterol for chronic asthma care in South Africa be conducted¹.

The current standard of care for chronic asthma therapy, in the Adult Hospital and Primary Healthcare STGs and EMLs, Respiratory chapters (2024) are for:

- *Infrequent asthma symptoms < twice a month (mild intermittent asthma)*: short-acting beta2 agonist (SABA) + ICS as needed (separate inhalers).
- *Asthma symptoms ≥ twice a month (mild persistent asthma)*: daily low dose ICS as controller therapy, and SABA as needed; and
- *Asthma symptoms almost daily or waking due to asthma ≥ once a week (moderate asthma)*: daily medium dose ICS/LABA as controller therapy, and SABA as needed.

The 2024 GINA guidelines recommend ICS/formoterol across the entire asthma disease spectrum, as shown in Track 1 (“controller and preferred reliever”) in Figure 1, below.

Note: GINA does not recommend concomitant use of salmeterol and formoterol-containing formulations due to lack of evidence.

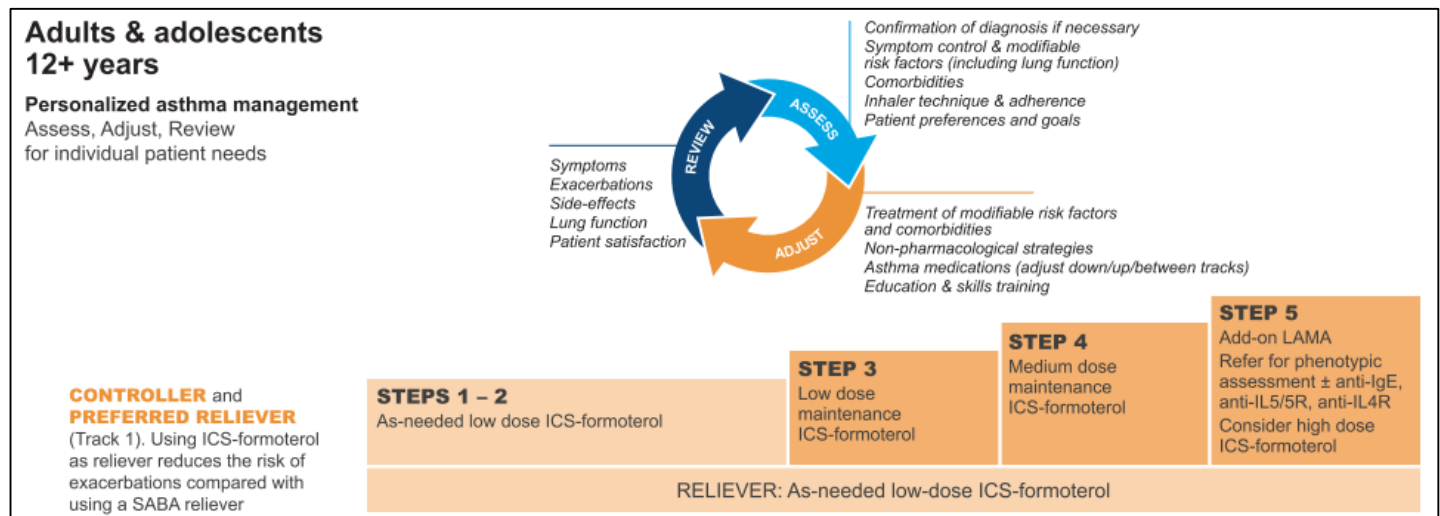


Figure 1: Personalized management for adults and adolescents to control symptoms and minimize risk

ICS = inhaled corticosteroid; LABA = long-acting β 2-agonist; LAMA = long-acting muscarinic antagonist; SABA = short-acting β 2-agonist

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This budget impact analysis (BIA), conducted from the payer’s perspective, evaluates the affordability of adopting ICS/formoterol for adolescents and adults with asthma in the South African public sector, compared to the current standard of care.

¹ Minutes of the NEMLC meeting of 29 August 2024

Technology under review

Table 1: Health technology being assessed

		Source
Acquisition cost (ZAR)		
• Formoterol/ budesonide 160/4.5 mcg inhaler (60 doses)	ZAR 59.47	Contract circular HP07-2023DAI
Method of administration	Inhalation	2024 GINA guidelines
Dosage	1 inhalation as needed	2024 GINA guidelines
Average length of a course of treatment	As needed	2024 GINA guidelines
Anticipated average interval between courses of treatments	Long-term treatment	
Anticipated number of repeat treatments	Long-term treatment	
Dose adjustments	n/a not modelled	

Table adapted from the NICE budget impact analysis template

This study includes:

- I. A secondary data analysis to estimate South African prevalence of asthma and Chronic Obstructive Pulmonary Disease (COPD), as well as utilisation of ICS/LABA, ICS and SABA inhalers in the South African public sector to establish the status quo situation in terms of treatment coverage.
- II. An incremental budget impact analysis.

The SAMRC Human Research Ethics Committee waived the requirement for informed consent for this analysis, which utilised secondary data sources, including delinked, anonymised records from the Western Cape Department of Health and aggregated utilisation data from the National Department of Health. Permission to use anonymised data was also granted by the Western Cape Provincial Health Data Centre.

Prevalence and utilisation data analysis

Methods

We sourced overall asthma, severe asthma and chronic obstructive pulmonary disease (COPD) prevalence estimates in South Africa from available published literature. This information was triangulated where possible and compared with expert opinion. We sourced disaggregated prevalence estimates for children, adolescents and adults, where relevant. However, due to the lack of patient registries for asthma and national electronic health records, there is a paucity of local prevalence estimates for mild persistent and mild intermittent asthma. Prevalence estimates were thus extrapolated from utilisation data sourced from national utilisation/procurement data, and national public-sector tender estimates, and triangulated against utilisation data from the Central Chronic Medicines Dispensing and Distribution (CCMDD) and Western Cape Central Dispensing Unit (CDU).

Assumptions

The following assumptions were made to estimate current utilisation:

1. All prescribers, dispensers and patients comply with the STGs and EML which guide asthma management for paediatrics, adolescents and adults in the South African public sector.
2. No stockouts requiring substitution.
3. SABA inhaler use for the management of acute asthma attacks is assumed to be negligible noting paucity of data to determine usage in this setting.
4. Proportion of patients on moderate-high dose and low-dose LABA/ICS sourced from the national utilisation data (estimated as 60.5% and 39.5% respectively)
5. Number as inhalers as per the standard of care arm in the BIA (see Table 4)
6. Severe asthma prevalence for adults was assumed to be 4% guided by expert opinion.

Current inhaler utilisation for moderate asthma was estimated by modelling chronic use of ICS/LABA inhalers as controller therapy for asthma, less the estimated proportion of these inhalers used for COPD (based on prevalence estimates of COPD as outlined below). For mild persistent asthma, current inhaler consumption was derived from regular use of ICS inhalers. For the mild intermittent asthma scenario, the utilisation of SABA inhalers was modelled by subtracting the estimated use for COPD, moderate adult asthma, and paediatric asthma.

Given the uncertainty surrounding these variables, sensitivity analyses were conducted.

Results

a: Prevalence of asthma and COPD

Asthma

There is limited data on the current prevalence of asthma among adults in South Africa (Lion-Cachet, 2021). The 2012 World Health Survey reported that 6.09% of South Africans aged 18-45 years reported clinically diagnosed asthma with symptoms, while the rate of doctor-diagnosed asthma was 5.92% (To, 2012). Subsequently, there have been no further population studies in South Africa. However, a systematic review in the African region indicated a self-reported wheezing rate of 13.25% (95% CI 10.5 to 16.5) among individuals aged 5 to 69 years and a physician-diagnosed asthma rate of 11.3% (9.0 to 14.1) (Song, 2022).

The self-reported symptoms of asthma among adolescents rose from 16.0% in the 1995 ISAAC Phase 1 study (Zar, 2007) to 21.3% in the 2017 GAN Phase 1 study (Baard, 2021). Similarly, diagnosed asthma prevalence increased from 13.1% (Zar, 2007) to 16.6% over the same period (Baard, 2021). There is a paucity of data on severe asthma prevalence in South African adults. Importantly, South Africa had the third highest age-standardized asthma mortality rates globally for 2011-2015 (Global Asthma Report, 2022).

Notably, the definitions for asthma and methodology to estimate asthma are variable across countries and globally definitions and denominators need standardisation (Quint, 2024).

COPD

ICS/LABA, LABA, and SABA inhalers are also indicated for chronic obstructive pulmonary disease (COPD), and two systematic reviews (Adeloye, 2022; Awokola, 2022) reported South African prevalence rates of 8%, largely based on the BOLD study (Buist, 2007). Studies suggest that the age onset of COPD is ≥ 40 years (Buist, 2007; Jarhyan, 2022). From the COPD Gene cohort study, we estimated that the proportion of COPD patients who may be eligible for an ICS/LABA in our setting is 26.7%, translating to a prevalence of 2.14 % (Criner, 2019; Ramkrishan, 2024) (see Table 2)

Table 2: Asthma and COPD prevalence estimates for the BIA models

Population group		Lower	Base-model	Upper	References
<i>Children</i>	Overall asthma	9%	11.20%	13%	Wichman 2007
	Severe asthma	4%	5.70%	8%	Wichman 2007
<i>Adolescents</i>	Overall asthma	17%	22%	27%	Baard 2020; Mphahlele 2023
	Severe asthma (% of study sample)	6%	8%	10%	Baard 2020; Mphahlele 2023; Asher 2021; Chung 2014
	Severe asthma (% of current asthma)		55%		Baard 2020
	Severe asthma (% of current asthma)		66%		Mphahlele 2023
<i>Adults</i>	Overall asthma	6%	10%	14%	To 2012; Zar 2013; Song 2022
	Severe asthma	1%	4%	7%	Expert opinion
	COPD	6%	8%	11%	Adeloye 2022; Awokola 2022; Buist 2007
	COPD Group E blood eosinophils $\geq 300/\mu\text{L}$	1.60%	2.14%	2.94%	Ramikrishan 2024; Criner 2019

See Appendix A for a summary of available prevalence studies.

b: Eligible population and current proportion accessing treatment (treatment coverage)

Eligible population

Approximately 85.88% of the uninsured adolescent and adult asthmatic population in South Africa, use public sector services (StatsSA 2004; CMS 2022/3). Although routine clinical management for all people with asthma is ideal, only a proportion of people access treatment.

Proportion of people with asthma who currently access treatment (treatment coverage)

The South African target adolescent/adult population for mild intermittent to severe asthma for 2024 was estimated to be 10.958 million people, and those accessing public-sector care were estimated to be 606,000. The estimated disaggregated target population and status quo treatment coverage estimates for mild intermittent asthma (PICO 1) were 4,576,000 and 279,000; mild persistent asthma (PICO 2) were 4,576,000 and 280,000; and moderate asthma (PICO 3) were 1,806,000 and 47,000, respectively (see Table 3). See Appendix B for the comparative analysis of the different utilisation datasets.

The estimated treatment coverage for the status quo scenario (modelled using the National Department of Health National Surveillance data (procurement data) for 1 June 2023 to 31 July 2024 and available asthma prevalence rates) and for the target population are described in Table 3).

Table 3: Treatment coverage for 1) status quo (based on utilisation data); 2) ideal treatment coverage (100% of estimated population with asthma)

STATUS QUO & IDEAL TREATMENT COVERAGE				Uninsured total population	Adolescents	2961809
					Adults	39235760
PICO 1						
	<i>Uptake rate</i>	<i>Prevalence</i>	<i>Currently treated population (n)</i>	<i>Rounded up/ down</i>	<i>Population (100%)</i>	<i>Rounded up/ down</i>
Adolescents	6,35%	22%	41405	41000	651598	652000
Adults	6,07%	10%	238152	238000	3923576	3924000
Total				279000		4576000
PICO 2						
	<i>Uptake rate</i>	<i>Prevalence</i>	<i>Currently treated population (n)</i>	<i>Rounded up/ down</i>	<i>Population (100%)</i>	<i>Rounded up/ down</i>
Adolescents	6,11%	22%	39821	40000	651598	652000
Adults	6,11%	10%	239779	240000	3923576	3924000
Total				280000		4576000
PICO 3						
	<i>Uptake rate</i>	<i>Prevalence</i>	<i>Currently treated population (n)</i>	<i>Rounded up/ down</i>	<i>Population (100%)</i>	<i>Rounded up/ down</i>
Adolescents	2,61%	8%	6180	6000	236945	237000
Adults	2,61%	4%	40935	41000	1569430	1569000
Total				47000		1806000
TOTAL POPULATION FOR PICOS 1,2,3:						
<i>Model (PICOs 1,2,3)</i>			<i>Status quo (PICOs 1,2,3)</i>	606000	<i>100% Uptake (PICOs 1,2,3)</i>	10958000

Budget impact analysis

Methods

Analytic framework, time horizon and perspective

The National Department of Health Technology Assessment Methods Guide (NDoH, 2023), the NEMLC-approved scoping report and ISPOR guidance for BIA (Sullivan, 2014) guided the static BIA modelling frameworks. The BIAs were conducted from the national public sector payer's perspective and considered 2024 pharmaceutical and healthcare costs.

Intervention(s) and comparator(s)

The intervention under review is budesonide/formoterol 160/4.5 mcg per inhalation, a 60-dose dry powder turbuhaler device, used as needed and, in moderate asthma used daily as part of the MART strategy. The agent is listed on the public sector contract (Contract circular HP07-2023DAI, 2023). Dosing was aligned with respective trial data, sourced from systematic reviews and where this was lacking, guided by expert opinion.

The comparator/s listed for PICO 1, 2 and 3 were aligned with the current standard of care, as described in the PICO summary, clinical trial data and drug utilisation data which was confirmed by experts.

Eligible populations and uptake

The **status quo scenario** was based on the estimated adolescent/adult asthmatic population accessing treatment in the public sector (treatment coverage) using current utilisation and prevalence estimates sourced from the published literature, as per the analysis above.

Implementation scenarios were costed for both **slow- and rapid-adoption scenarios**. The slow-adoption scenario assumes limited prescribing and uptake of ICS/formoterol therapy (10% transition to ICS/formoterol strategy per year). This may be due to training required for both the patient and healthcare professionals. The rapid-adoption scenario (20% transition per year) assumes that there are few or no delays in supply and that eligible patients will access the medicine/s where indicated. Guidance was sought from clinical pulmonology experts to estimate the uptake rates for the two implementation scenarios, with assumptions described and referenced.

Resources

As per the HTA Methods Guide (NDoH, 2023), only direct health costs from the payer's perspective with an expected difference between the proposed medicine/s and comparator/s, and direct health care utilisation costs were presented. Costs assumed to be the same for the interventions and comparator were not presented as they will not affect the decision to include/exclude the medicine from the EML.

Medicine costs were sourced from public sector pharmaceutical contract prices. Estimates of as-needed reliever therapy as either ICS/formoterol or SABA were costed for the BIA model - sourcing the cumulative doses of formoterol/ICS or SABA reliever therapy from the available evidence.

Inpatient day estimates for hospital costs were sourced from secondary data rather than derived from an ingredients approach.

Costs were adjusted for inflation to current 2024 costs, where required.

Assumptions

1. Wastage factor for salbutamol 0.5% 20 ml inhalation solution for acute asthma attacks was estimated as 25%.
2. Administration sets, syringes and other consumables have not been costed, as this was assumed to have little potential effect on the model.
3. Patients with moderate asthma in the ICS/formoterol arm of the model are assumed to be controlled on formoterol/budesonide 160/4.5 or 320/9 mcg inhalation twice a day (currently the cheapest ICS/LABA formulation on public sector tender).
4. During emergency transport from the clinic to the hospital for severe asthma exacerbation, only basic life support has been costed. Distance from the clinic to the hospital emergency room is assumed to be less than 50 km.
5. Cost for PHC clinic visit has been extrapolated from Uniform Patient Fee Schedule port health and travel clinic fee, and assuming 10% (5% to 15%) of people with asthma who present at the PHC level would require referral to a hospital for management, and 90% would be controlled through PHC services.
6. For mild intermittent asthma, systemic corticosteroids for severe exacerbation would require a clinic visit.
7. There is a paucity of effectiveness and safety data comparing inhaled ICS/SABA to ICS/formoterol in mild intermittent asthma, and experts recommended comparable efficacy and safety between these two agents in this clinical setting. Efficacy data was extrapolated from the ICS/formoterol group in the PICO 1 evidence review.
8. In the standard of care arm, inhaled corticosteroids as controller therapy dosed as 200 mcg (beclomethasone/budesonide) 12 hourly was assumed to be the standard dosing amongst adolescents/adults, with 3x budesonide 200 mcg (300 doses) and 4x beclomethasone 200 mcg (200 doses) inhalers used per annum – assuming that 85.5% on beclomethasone and 14.5% on budesonide extrapolated from national utilisation data.
9. For moderate asthma, it was assumed that 60.5% of patients use budesonide/formoterol 160/4.5 mcg and 39.5% use budesonide/formoterol 320/9 mcg extrapolated from national utilisation data.
10. Hospital costs were extrapolated from unpublished data collected by HE2RO, shared in confidence and awaiting publication (at the time of undertaking this analysis).
11. The rate of ICU admission for adults/adolescents with moderate asthma was assumed to be 3% (2%, 4%) based on expert opinion (noting that the ICU admission rate amongst children, reported in a recent thesis was 1.2%), with a length of ICU stay of three days, extrapolated from Manyeruke et al (Manyeruke, 2023). For mild persistent asthma, no patients were assumed to be admitted to ICU.
12. For adults and adolescents with mild intermittent asthma, 10% (5%-15%) of patients visiting the emergency room were assumed to require a hospital stay.
13. Length of hospital stay in the general ward was assumed to be two days extrapolated from Manyeruke et al (Manyeruke, 2023).
14. For moderate asthma, all deaths occur in the ICU.
15. Among adolescents and adults, a spacer was not included in the cost analysis.
16. Stats SA population growth of 1.3% was applied to years 2-5 for patients receiving treatment.
17. Discount rate of 3% was applied to future costs from years 2-5.
18. For the BIA model of 1000 patients, we assumed the health states to be as outlined in the PICO summary above, and assumed all patients were adult males weighing 70 kg.

Number of inhalers

The number of inhalers required per annum was estimated using effectiveness trial data and the STGs and EML with pragmatic consideration of Chronic Medicines Dispensing data CCMDD and WC CDU (see Appendix C), confirmed by expert opinion. Of note is that a single fixed-dose combination inhaler of ICS with SABA is currently not available on the South African market and therefore, one SABA inhaler plus one ICS inhaler was assumed to be dispensed per prescription for PICO 1 (mild intermittent asthma). For mild intermittent asthma (PICO 1), wastage could not be quantified. In PICO 2, wastage estimates were applied to beclometasone (38%), budesonide (45%), salbutamol (40%), and budesonide/formoterol 160/4.5 mcg (32%) based on CDU data and expert opinion. In PICO 3, wastage was assumed to be 0% for budesonide/formoterol maintenance inhalers and 40% for salbutamol. The numbers of inhalers used in the models are summarised in Table 4.

Table 4: Number of inhalers per annum used in the BIA models for each PICO.

Population	Intervention inhalers per annum	Comparator inhalers per annum	Evidence
Mild intermittent asthma (step 1)	- ICS/formoterol as needed - Bud/form 160/4.5mcg: 3	- ICS as needed - Bud 200mcg (300 doses): 2 - Beclo 200mcg (200 doses): 2 - SABA as needed: 2	Expert opinion
Mild persistent asthma (step 2)	- ICS/formoterol as needed - Bud/form 160/4.5mcg: 6	- ICS maintenance - Bud 200mcg (300doses): 4 - Beclo 200mcg (200 doses): 3 - SABA as needed: 6	Hatter et al (2021). Western Cape Chronic Dispensing Unit data
Moderate asthma (steps 3-4)	- ICS/formoterol maintenance - Bud/form 160/4.5 mcg: 12 OR - Bud/form 320/9 mcg: 12 PLUS - ICS/FABA as needed - Bud/form 160/4.5mcg: 6	- ICS/LABA maintenance - Bud/form 160/4.5 mcg: 12 OR - Bud/form 320/9 mcg: 12 PLUS - SABA as needed: 6	As needed reliever therapy estimates extracted from RCTs included in the PICO 3 rapid review. Western Cape Chronic Dispensing Unit data
Abbreviations: Beclo=beclomethasone (metered-dose inhaler); Bud=budesonide (metered dose inhaler); Bud/form=budesonide/formoterol (60 doses, dry powder inhaler); ICS=inhaled corticosteroid; FABA=fast-acting- β 2-agonists; MART=maintenance-and-reliever therapy; SABA=short-acting- β 2-agonist (salbutamol 100mcg, 200 doses, metered dose inhaler).			

Sensitivity analyses

As local epidemiological data is limited, uncertainties in this static BIA analysis were addressed with sensitivity analyses, varying the value of variables included in the baseline BIA analysis, as appropriate for each asthma severity group. These include the medicine price of ICS/formoterol, as-needed SABA use for PICO 2 and 3, the number of inhalers (for ICS/formoterol and standard of care) for PICO 1, PHC visits and hospitalisation costs, the proportion of patients requiring upward referrals from PHC facilities, estimates and uptake rates in the public sector (using the various implementation scenarios, described above). We also estimated a threshold price for budesonide/ formoterol 160/4.5 mcg, by determining price parity between the intervention and standard of care.

Models

A static probabilistic decision model was used to estimate the incremental budget impact for a cohort of 1000 patients. TreeAge Pro® 2024 software was used to compute the BIA model.

PICO 1: mild intermittent asthma

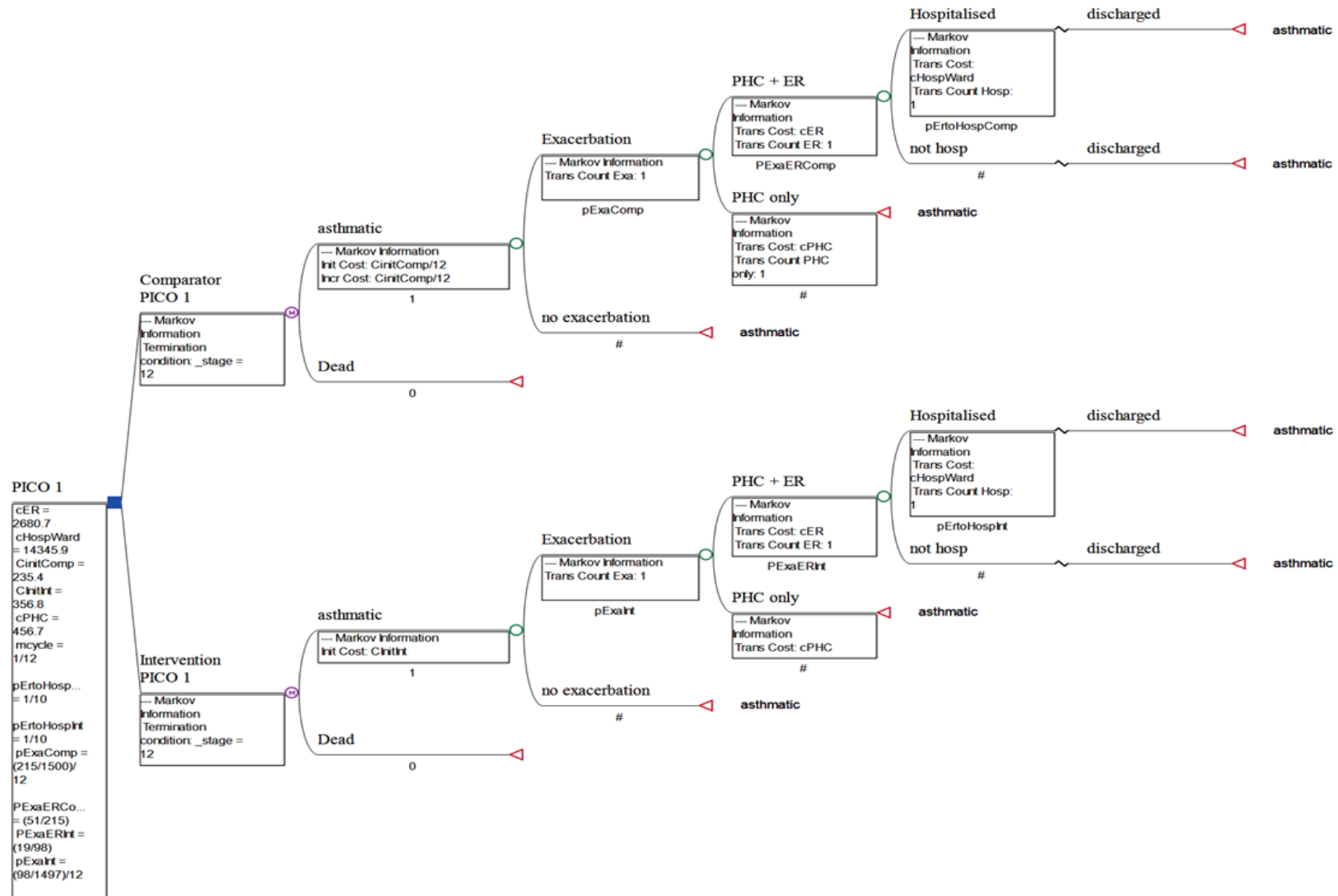


Figure 2: BIA model for mild intermittent asthma

PICO 2: mild persistent asthma

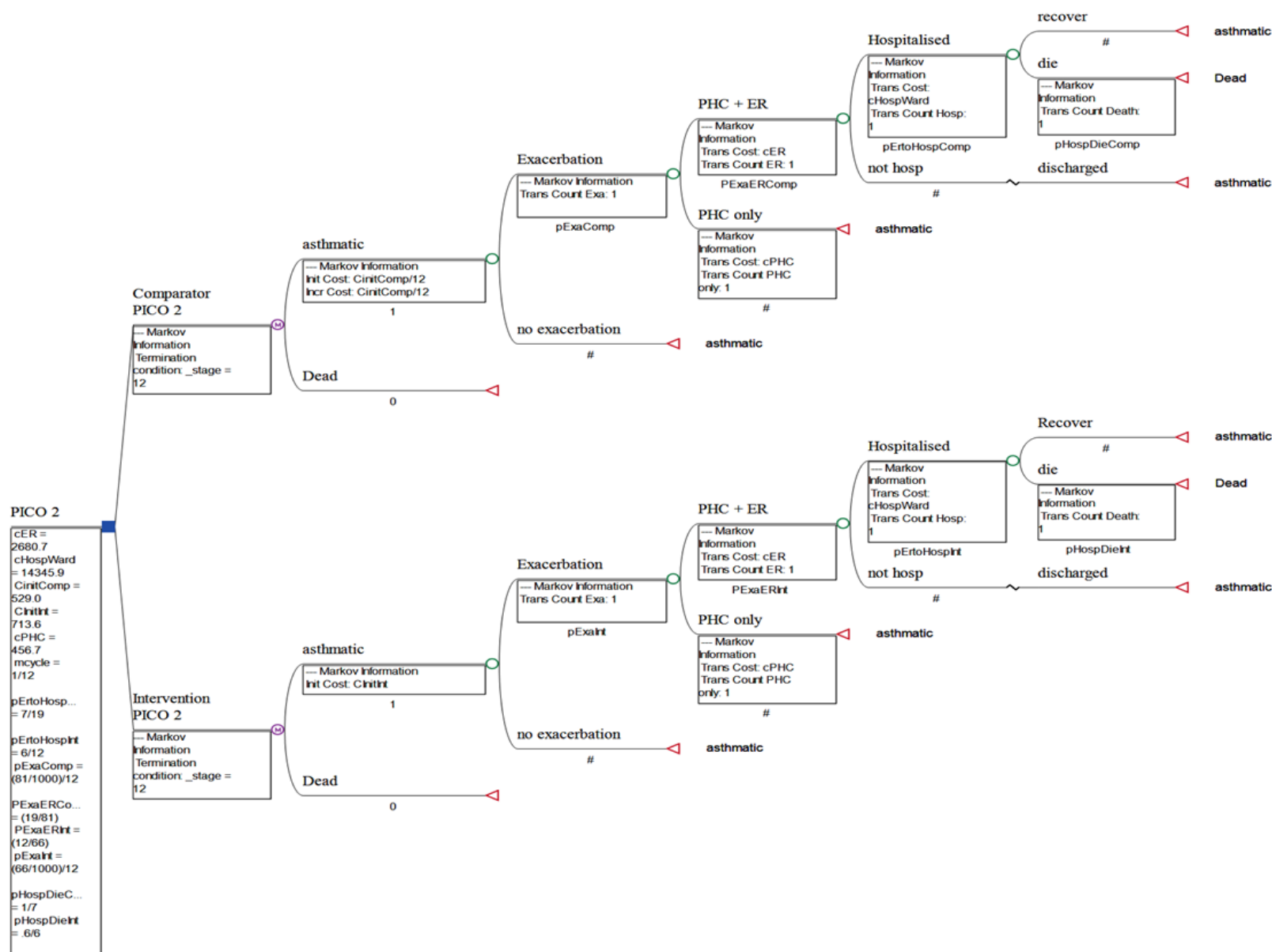
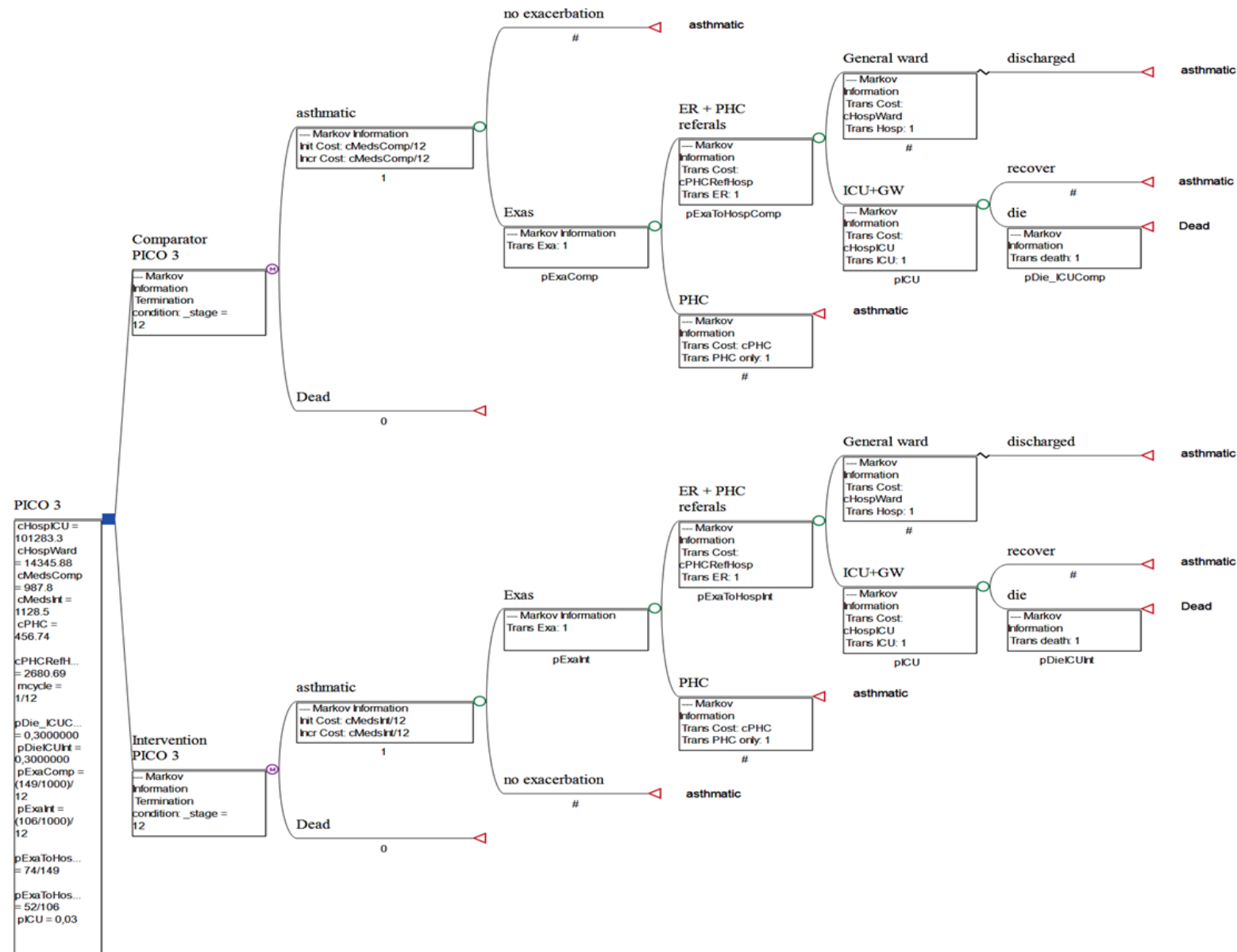


Figure 3: BIA model for mild persistent asthma

PICO 3: moderate persistent asthma



Resources

Healthcare resources

Healthcare resources associated with the use of ICS/formoterol inhalers (aligned with 2024 GINA guidelines) include staff costs, diagnostic and monitoring costs, facility costs and referral transport costs. These resources would also apply to current clinical practice. An ingredient approach was used to estimate the costs for primary healthcare clinic visits (sourced from public sector tenders, National Department of Health, Uniform Patient Fee Schedule 2024, and buy-out price on file at NDoH for non-tender medicine prices); whilst hospitalisation cost data was extrapolated from data collected by HE²RO on hospital costs during COVID-19 (HE²RO, 2019), inflated to 2024 ZAR. Table 5 presents the unit costs for 12 months.

Table 5: Unit costs for ICS/formoterol and standard of care

Cost type	Cost (ZAR)	Unit
ICS/formoterol		
Acquisition costs		Per person per course of treatment per year (ZAR)
<i>PICO 1:</i>		
• Budesonide/formoterol 160/4.5mcg (60 doses) x3	@59.47	178.41
<i>PICO 2:</i>		
• Budesonide/formoterol 160/4.5mcg (60 doses) x6	@59.47	356.82
<i>PICO 3:</i>		
• Budesonide/formoterol 160/4.5mcg (60 doses) x18, OR	@59.47	1070.46
• Budesonide/formoterol 320/9mcg (60 doses) x12 PLUS	@67.64	1168.50
• Budesonide/formoterol 160/4.5mcg (60 doses) x6	@59.47	
Healthcare resource use		Per person per event
• Primary healthcare clinic visit		429.72 (411.13, 475.28)
• Primary healthcare clinic visit, with referral to hospital		2441.72 (2396.18, 2487.30)
• Hospital emergency room visit		2436.52 (2037.68, 3982.19)
• General ward hospital admission		7172.94 (6953.76, 7399.39)
• ICU admission		28979.13 (28063.74, 30087.49)
Standard of Care		
Acquisition costs		Per person per course of treatment per year
<i>PICO 1:</i>		
• Beclomethasone 200mcg (200 doses) x2	@72.01	Beclomethasone 200mcg + SABA: 183.26*
• Budesonide 200 mcg (300 doses) x2	@72.22	Budesonide 200 mcg + SABA: 183.68*
• Salbutamol 100mcg (200 doses)** x2	@19.62	
<i>PICO 2:</i>		
• Beclomethasone 200mcg (200 doses) x4	@72.01	Beclomethasone 200mcg + SABA: 405.76
• Budesonide 200 mcg (300 doses) x3	@72.22	Budesonide 200 mcg + SABA: 334.38
• Salbutamol 100mcg (200 doses)** x6	@19.62	
<i>PICO 3:</i>		
• Budesonide/formoterol 160/4.5mcg (60 doses) x12	@59.47	Low-dose ICS/LABA + SABA as needed: 831.36
• Budesonide/formoterol 320/9mcg (60 doses) x12	@67.64	High-dose ICS/LABA + SABA as needed: 929.40
• Salbutamol 100mcg (200 doses)** x6	@19.62	

Healthcare resource use		Per person per event
• Primary healthcare clinic visit		429.72 (411.13, 475.28)
• Primary healthcare clinic visit, with referral to hospital		2441.72 (2396.18, 2487.30)
• Hospital emergency room visit		2436.52 (2037.68, 3982.19)
• General ward hospital admission		7172.94 (6953.76, 7399.39)
• ICU admission		28979.13 (28063.74, 30087.49)

*ICS/SABA combination inhaler is not available on the South African market, thus 1x SABA inhaler + 1x ICS inhaler per prescription was costed.

**Salbutamol 100mcg (200 doses) = SABA

Adverse events

The adverse events reported in the studies were similar between the formoterol/ICS inhaler (the intervention) and the standard of care (the control). For patients with mild persistent asthma, asthma-related events and deaths were among the reported adverse events. However, these were also assessed as separate outcomes, so they were not included in the overall adverse event count.

Efficacy: i.e. events avoided

Anticipated savings (or events avoided) associated with ICS/formoterol relate to severe exacerbations, emergency room visits, and hospitalisation compared to standard of care (see Table 6).

Table 6: Efficacy estimates of ICS/formoterol compared with standard of care treatment

1. PICO 1 (Refer to the medicine review for PICO 1 for detailed information)						
Note: 1) There is a paucity of data for the efficacy and safety of ICS+SABA compared to ICS/formoterol for mild intermittent asthma. Based on expert opinion, it was assumed that the efficacy and safety of ICS+SABA were comparable to ICS/formoterol. Evidence: Expert opinion; <i>very low certainty evidence</i>						
2. PICO 2 (Refer to the medicine review for PICO 2 for detailed information)						
Outcomes	Anticipated absolute effects* (95% CI)		NNT	Relative effect (95% CI)	n (studies)	Certainty of the evidence (GRADE)
	Risk with daily low-dose ICS +SABA reliever	Risk with formoterol + ICS as needed				
Acute severe exacerbations requiring systemic steroid: follow-up 52 weeks	81 per 1,000	66 per 1,000 (49 to 87)	67	RR 0.81 (0.61 to 1.07)	8065 (4 RCTs)	⊕⊕⊕○ Moderate ^{a,b}
Asthma-related visits to the emergency room: follow-up 52 weeks	19 per 1,000	12 per 1,000 (9 to 18)	143	RR 0.65 (0.46 to 0.93)	8065 (4 RCTs)	⊕⊕⊕⊕ High ^{a,c}
Asthma-related hospital admissions: follow-up 52 weeks	7 per 1,000	6 per 1,000 (4 to 11)	1000	RR 0.88 (0.50 to 1.53)	7620 (3 RCTs)	⊕⊕⊕⊕ High ^{a,c}
Evidence: PICO 2 rapid review; <i>moderate certainty evidence</i>						

3. PICO 3

(Refer to the medicine review for PICO 3 for detailed information)

Outcomes	Anticipated absolute effects* (95% CI)		NNT	Relative effect (95% CI)	n (studies)	Certainty of the evidence (GRADE)
	Risk with ICS/LABA maintenance therapy + as needed SABA reliever therapy	Risk with ICS/formoterol maintenance therapy + as needed reliever therapy				
Severe Asthma Exacerbation	149 per 1,000	106 per 1,000 (97 to 115)	24	RR 0.71 (0.65 to 0.77)	17376 (10 RCTs)	⊕⊕⊕⊕ High ^a
Systemic Corticosteroid Use	134 per 1,000	92 per 1,000 (80 to 107)	25	RR 0.69 (0.60 to 0.80)	9436 (4 RCTs)	⊕⊕⊕⊕ High ^b
Asthma-related visits to the ER and/or hospital admissions	74 per 1,000	52 per 1,000 (46 to 59)	46	RR 0.70 (0.62 to 0.80)	14136 (7 RCTs)	⊕⊕⊕⊕ High ^b
Asthma-related visits to the ER	145 per 1,000	107 per 1,000 (85 to 135)	27	RR 0.74 (0.59 to 0.93)	2091 (1 RCT)	⊕⊕⊕○ Moderate ^{b,c}
Asthma-related hospital admissions	29 per 1,000	11 per 1,000 (5 to 25)	56	RR 0.39 (0.18 to 0.85)	2394 (2 RCTs)	⊕⊕⊕○ Moderate ^{b,c}
Mortality	1 per 1,000	1 per 1,000 (0 to 2)	0	RR 0.77 (0.25 to 2.33)	14136 (7 RCTs)	⊕⊕⊕⊕ High ^{b,d}

Evidence: PICO 3 rapid review; *moderate certainty evidence*

Abbreviations: BIA=budget impact analysis, ICS=inhaled corticosteroid, LABA=long-acting b2 agonist, n=number of study participants, NNT=number needed to treat, RCT=randomised controlled trial, SABA=short-acting b2 agonist

Results

Estimates of annual incremental budget impact

The target adolescent/asthma population with mild to moderate asthma to be treated with the ICS/formoterol strategy was estimated to be 10.958 million, while coverage with the current standard of care in the South African public sector was estimated to be 606,000 (status quo).

Total annual costs (pharmaceutical and non-pharmaceutical costs), from the payer perspective, were estimated to be R10,155,093,096 for the current status quo population receiving standard of care scenario compared to R10,469,994,035 for ICS/formoterol. This will result in an additional cost of R314,900,939 over 1 year (see Table 10).

This total budget impact of implementing ICS/formoterol over standard of care includes increased pharmaceutical costs (R232,754,939) and non-pharmaceutical costs (R82,146,000). Pharmaceutical costs were higher for ICS/formoterol for PICO 3, but lower for PICOs 1 and 2. In addition, healthcare resource use costs (mostly hospitalisation) were significantly lower for ICS/formoterol for PICO 3. The disaggregated estimates for mild intermittent (PICO 1), mild persistent (PICO 2) and moderate asthma (PICO 3) are described in Tables 7, 8 and 9.

PICO 1: mild intermittent asthma

Table 7: Estimated budget impact for mild intermittent asthma

Comparator vs Intervention:	Model	Full Eligible population	Status quo	Year 1	Year 2	Year 3	Year 4	Year 5
Patient population that will receive the new technology	1000	4,576,000	279,000					
A: RAPID ADOPTION (20% per annum)								
Rapid implementation scenario (comparator)	100%	100%	100%	80%	60%	40%	20%	0%
Pharmaceutical costs	183,000	838,876,438	51,146,531	40,917,225	31,096,068	21,006,430	10,642,908	-
Healthcare resource use costs	533,000	2,439,008,000	148,707,000	118,965,600	90,410,882	61,075,564	30,943,935	-
Other costs/savings not captured elsewhere	n/a		n/a	n/a	n/a	n/a	n/a	n/a
Total cost of current treatment pathway	716,000	3,277,884,438	199,853,531	159,882,825	121,506,950	82,081,995	41,586,843	-
Rapid adoption implementation scenario (intervention)	100%	100%	100%	20%	40%	60%	80%	100%
Pharmaceutical costs	178,000	816,404,160	49,776,390	9,955,278	20,175,366	30,665,548	41,431,200	52,477,794
Healthcare resource use costs	762,000	3,486,912,000	212,598,000	42,519,600	86,170,221	130,974,428	176,955,184	224,135,860
Other costs/savings not captured elsewhere	n/a		n/a	n/a	n/a	n/a	n/a	n/a
Total cost of new treatment pathway	940,000	4,303,316,160	262,374,390	52,474,878	106,345,588	161,639,976	218,386,384	276,613,653
NET & incremental BUDGET IMPACT (future - current treatment pathway costs)	[224,000]	[1,025,431,722]	[62,520,859]	212,357,703	227,852,538	243,721,971	259,973,226	276,613,653
B: SLOW ADOPTION (10% per annum)								
Slow implementation scenario (comparator)	100%	100%	100%	90%	80%	70%	60%	50%
Pharmaceutical costs	183,000	838,876,438	51,146,531	46,031,878	41,461,424	36,761,253	31,928,724	26,961,147
Healthcare resource use costs	533,000	2,439,008,000	148,707,000	133,836,300	120,547,842	106,882,238	92,831,804	78,388,723
Other costs/savings not captured elsewhere	n/a		n/a	n/a	n/a	n/a	n/a	n/a
Total cost of current treatment pathway	716,000	3,277,884,438	199,853,531	179,868,178	162,009,266	143,643,491	124,760,528	105,349,869
Slow implementation scenario (intervention)	100%	100%	100%	10%	20%	30%	40%	50%
Pharmaceutical costs	178,000	816,404,160	49,776,390	4,977,639	10,087,683	15,332,774	20,715,600	26,238,897
Healthcare resource use costs	762,000	3,486,912,000	212,598,000	21,259,800	43,085,111	65,487,214	88,477,592	112,067,930
Other costs/savings not captured elsewhere	n/a		n/a	n/a	n/a	n/a	n/a	n/a
Total cost of new treatment pathway	940,000	4,303,316,160	262,374,390	26,237,439	53,172,794	80,819,988	109,193,192	138,306,827
NET BUDGET IMPACT (future - current treatment pathway costs)	[224,000]	[1,025,431,722]	[62,520,859]	206,105,617	215,182,060	224,463,479	233,953,720	243,656,696

Note: Costs are provided as South African Rands (ZAR).

PICO 2: mild persistent asthma

Table 8: Estimated budget impact for mild persistent asthma

Comparator vs Intervention:	Model	Full eligible population	Status quo	Year 1	Year 2	Year 3	Year 4	Year 5
Patient population that will receive the new technology	1000	4,576,000	280,000					
A: RAPID ADOPTION (20% per annum)								
Rapid implementation scenario (comparator)	100%	100%	100%	80%	60%	40%	20%	0%
Pharmaceutical costs	395,000	1,809,395,702	110,714,772	88,571,818	67,312,367	45,471,748	23,038,261	-
Healthcare resource use costs	178,000	814,528,000	49,840,000	39,872,000	30,301,723	20,469,824	10,371,036	-
Other costs/savings not captured elsewhere	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Total cost of current treatment pathway	573,000	2,623,923,702	160,554,772	128,443,818	97,614,090	65,941,572	33,409,297	-
Rapid adoption implementation scenario (intervention)	100%	100%	100%	20%	40%	60%	80%	100%
Pharmaceutical costs	357,000	1,632,808,320	99,909,600	19,981,920	40,495,359	61,550,921	83,159,398	105,331,772
Healthcare resource use costs	141,000	645,216,000	39,480,000	7,896,000	16,002,034	24,322,291	32,861,037	41,622,610
Other costs/savings not captured elsewhere	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Total cost of new treatment pathway	498,000	2,278,024,320	139,389,600	27,877,920	56,497,393	85,873,212	116,020,434	146,954,383
NET & incremental BUDGET IMPACT (future - current treatment pathway costs)	[-75,000]	[-345,899,382]	[21,165,172]	156,321,738	154,111,483	151,814,784	149,429,732	146,954,383
B: SLOW ADOPTION (10% per annum)								
Slow implementation scenario (comparator)	100%	100%	100%	90%	80%	70%	60%	50%
Pharmaceutical costs	395,000	1,809,395,702	110,714,772	99,643,295	89,749,823	79,575,558	69,114,783	58,361,675
Healthcare resource use costs	178,000	814,528,000	49,840,000	44,856,000	40,402,298	35,822,192	31,113,109	26,272,428
Other costs/savings not captured elsewhere	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Total cost of current treatment pathway	573,000	2,623,923,702	160,554,772	144,499,295	130,152,120	115,397,751	100,227,892	84,634,103
Slow implementation scenario (intervention)	100%	100%	100%	10%	20%	30%	40%	50%
Pharmaceutical costs	357,000	1,632,808,320	99,909,600	9,990,960	20,247,680	30,775,461	41,579,699	52,665,886
Healthcare resource use costs	141,000	645,216,000	39,480,000	3,948,000	8,001,017	12,161,145	16,430,518	20,811,305
Other costs/savings not captured elsewhere	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Total cost of new treatment pathway	498,000	2,278,024,320	139,389,600	13,938,960	28,248,696	42,936,606	58,010,217	73,477,191
NET BUDGET IMPACT (future - current treatment pathway costs)	[-75,000]	[-345,899,382]	[21,165,172]	158,438,255	158,400,817	158,334,357	158,238,109	158,111,294

Note: Costs are provided as South African Rands (ZAR).

PICO 3: moderate persistent asthma

Table 9: Estimated budget impact for moderate asthma

Comparator vs Intervention:	Model	Full eligible population	Status quo	Year 1	Year 2	Year 3	Year 4	Year 5
Patient population that will receive the new technology	1000	1,806,000	47,000					
A: RAPID ADOPTION (20% per annum)								
Rapid implementation scenario (comparator)	100%	100%	100%	80%	60%	40%	20%	0%
Pharmaceutical costs	870,000	1,571,374,955	40,894,033	32,715,226	24,862,754	16,795,619	8,509,500	-
Healthcare resource use costs	1,485,000	2,681,910,000	69,795,000	55,836,000	42,433,964	28,665,557	14,523,405	-
Other costs/savings not captured elsewhere	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Total cost of current treatment pathway	2,355,000	4,253,130,000	110,689,033	88,551,226	67,296,718	45,461,176	23,032,905	-
Rapid adoption implementation scenario (intervention)	100%	100%	100%	20%	40%	60%	80%	100%
Pharmaceutical costs	1,109,000	2,003,189,555	52,131,733	10,426,347	21,130,034	32,116,595	43,391,661	54,960,962
Healthcare resource use costs	1,044,000	1,885,464,000	49,068,000	9,813,600	19,888,242	30,229,133	40,841,574	51,730,959
Other costs/savings not captured elsewhere	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Total cost of new treatment pathway	2,153,000	3,888,653,555	101,199,733	20,239,947	41,018,276	62,345,728	84,233,235	106,691,921
NET & incremental BUDGET IMPACT (future - current treatment pathway costs)	[-202,000]	[-364,631,400]	[-9,489,300]	108,791,173	108,314,994	107,806,904	107,266,140	106,691,921
B: SLOW ADOPTION (10% per annum)								
Slow implementation scenario (comparator)	100%	100%	100%	90%	80%	70%	60%	50%
Pharmaceutical costs	870,000	1,571,374,955	40,894,033	36,804,629	33,150,339	29,392,333	25,528,501	21,556,692
Healthcare resource use costs	1,485,000	2,681,910,000	69,795,000	62,815,500	56,578,619	50,164,725	43,570,214	36,791,415
Other costs/savings not captured elsewhere	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Total cost of current treatment pathway	2,355,000	4,253,130,000	110,689,033	99,620,129	89,728,957	79,557,058	69,098,715	58,348,106
Slow implementation scenario (intervention)	100%	100%	100%	10%	20%	30%	40%	50%
Pharmaceutical costs	1,109,000	2,003,189,555	52,131,733	5,213,173	10,565,017	16,058,297	21,695,830	27,480,481
Healthcare resource use costs	1,044,000	1,885,464,000	49,068,000	4,906,800	9,944,121	15,114,567	20,420,787	25,865,479
Other costs/savings not captured elsewhere	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Total cost of new treatment pathway	2,153,000	3,888,653,555	101,199,733	10,119,973	20,509,138	31,172,864	42,116,617	53,345,961
NET BUDGET IMPACT (future - current treatment pathway costs)	[-202,000]	[-364,631,400]	[-9,489,300]	109,740,103	110,238,095	110,729,922	111,215,332	111,694,067

Note: Costs are provided as South African Rands (ZAR).

Table 10: Total costs for the eligible target population (PICO 1, 2 &3)

COMPARATOR	
• Total pharmaceutical costs	4,219,647,096
• Total healthcare resource use costs	5,935,446,000
Total costs	10,155,093,096
INTERVENTION	
• Total pharmaceutical costs	4,452,402,035
• Total healthcare resource use costs	6,017,592,000
Total costs	10,469,994,035
NET ADDITIONAL COST	
[314,900,939]	

The estimated budget impact for the BIA model with 1,000 patients was a net cost-saving of R53,401 but once implemented for patients currently accessing care (status quo) and for the total eligible population, additional cost is incurred, as shown in Table 11.

Table 11: Estimates of total annual incremental budget impact (PICO 1, 2, 3)

Population/ PICO	Costs	Model (1000)	Status quo	Total target population (100%)
Mild intermittent asthma / PICO 1	Net Pharmaceutical costs	-4,911	-1,370,141	-22,472,278
	Net-health care use costs	229,000	63,891,000	1,047,904,000
	NET BUDGET IMPACT	224,089	62,520,859	1,025,431,722
Mild persistent asthma/ PICO 2	Net Pharmaceutical costs	-38,590	-10,805,172	-176,587,382
	Net-health care use costs	-37,000	-10,360,000	-169,312,000
	NET BUDGET IMPACT	-75,590	-21,165,172	-345,899,382
Moderate asthma/ PICO 3	Net Pharmaceutical costs	239,100	11,237,700	431,814,600
	Net-health care use costs	-441,000	-20,727,000	-796,446,000
	NET BUDGET IMPACT	-201,900	-9,489,300	-364,631,400
TOTAL ADOLESCENT/ ADULT POPULATION (GINA steps 1-4)	Net Pharmaceutical costs	195,599	-937,613	232,754,939
	Net-health care use costs	-249,000	32,804,000	82,146,000
	NET BUDGET IMPACT TOTAL	(53,401)	31,866,387	314,900,939

Table 12 summarises the annual cost per person comparisons of ICS/formoterol compared to standard of care across the various asthma severities

Table 12: Overview of the annual per-patient cost comparisons of ICS/formoterol vs standard of care across asthma severities

Intervention	Total intervention cost (pharmaceutical + healthcare use)	Comparator	Total comparator cost (pharmaceutical + healthcare use)
PICO 1: Mild intermittent asthma			
ICS/formoterol (budesonide/formoterol 160/4.5mcg) as needed	R940 (R178 + R7625)	ICS (budesonide/ beclometasone 200mcg) as needed + SABA as needed	R716 (R183 + R533)
PICO 2: Mild persistent asthma			
ICS/formoterol (budesonide/formoterol 160/4.5mcg) as needed	R498 (R357 + R141)	ICS (budesonide/ beclometasone 200mcg) 12 hourly + SABA as needed	R573 (R395 + R178)
PICO 3: Moderate asthma			
ICS/formoterol (budesonide/formoterol 160/4.5mcg or 320/9mcg) 12 hourly as controller therapy + ICS/FABA (budesonide/formoterol 160/4.5mcg) as needed	R2153 (R1109 + R1044)	ICS/LABA (budesonide/ formoterol 160/4.5mcg or 320/9mcg) 12-hourly as controller therapy + SABA as needed	R2355 (R870 + R1485)

SABA = salbutamol 100mcg inhaler, 200 doses, dosed as 200mcg as needed to a maximum daily dose of 800 mcg.

Budgetary implications of rapid compared to slow adoption scenarios

The analysis highlights the budgetary implications of transitioning patients from the current standard of treatment to the new treatment regimen under two adoption scenarios: rapid and slow. In the rapid adoption scenario, 20% of patients transition annually to the ICS/formoterol strategy, resulting in full adoption by Year 5. In contrast, the slow adoption scenario transitions 10% of patients annually, with 50% remaining on the current standard of treatment by the end of Year 5. In both scenarios, net costs are assessed relative to maintaining all patients on the current standard of care.

This analysis accounts for annual population growth, resulting in an incremental increase in the treatment population each year. However, it does not assume improvements in programmatic coverage to reach the full eligible population living with asthma. As a result, the budgetary implications reflect costs for patients currently on treatment, without expanding coverage to untreated individuals who may benefit from the intervention.

Rapid adoption scenario

In the rapid adoption scenario, pharmaceutical costs exhibit varying trends across the three PICO groups. For PICO 1, pharmaceutical costs initially decrease compared to the standard of care scenario, with a net saving of R274,028 in Year 1, increasing to R1.44 million by Year 5. However, total healthcare costs increase significantly over time. PICO 2 follows a similar trend, with pharmaceutical costs decreasing by R2.16 million in Year 1 and accumulating to R11.39 million in savings by Year 5. Additionally, healthcare costs decline, suggesting overall cost savings in this group. Conversely, PICO 3 experiences increased pharmaceutical spending, with costs rising by R2.25 million in Year 1 and reaching R11.85 million by Year 5, though healthcare costs decline.

When aggregated, the net pharmaceutical cost difference across all groups shows an initial reduction of R187,523 in Year 1, increasing to R988,498 by Year 5 in favour of ICS/formoterol. However, this is offset by healthcare cost increases, particularly in PICO 1.

Slow adoption scenario

Under the slow adoption scenario, pharmaceutical cost reductions are more gradual. In PICO 1, savings start at R137,014 in Year 1 and grow to R722,250 by Year 5. PICO 2 also experiences pharmaceutical cost reductions, saving R1.08 million in Year 1 and accumulating R5.70 million by Year 5. In contrast, PICO 3 sees an increase in pharmaceutical spending, similar to the rapid adoption scenario, with costs rising by R1.12 million in Year 1 and reaching R5.92 million by Year 5.

The overall net pharmaceutical cost savings under the slow adoption scenario is R93,761 in Year 1, increasing to R494,249 by Year 5, which is smaller than the savings observed under the rapid adoption approach.

Key insights

- PICO 1 and PICO 2 show pharmaceutical cost savings in both adoption scenarios, but PICO 3 leads to increased pharmaceutical costs under both strategies.
- Healthcare costs increase in PICO 1 under rapid adoption, which offsets pharmaceutical savings, whereas PICO 2 sees both pharmaceutical and healthcare savings, making it the most cost-effective shift.
- The rapid adoption scenario results in greater overall pharmaceutical cost savings (R988,498 by Year 5) compared to the slow adoption scenario (R494,249 by Year 5).

Table 13: Difference in costs for the rapid compared to slow adoption scenarios

Rapid adoption scenario: SoC/ICS/formoterol use	100%/0%	80%/20%	60%/40%	40%/60%	20%/80%	0%/100%
	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
PICO 1 Total Pharmaceutical Costs Rapid Uptake	R51,146,531	R50,872,503	R51,271,434	R51,671,979	R52,074,108	R52,477,794
PICO 1 Total Healthcare Costs Rapid Uptake	R148,707,000	R161,485,200	R176,581,103	R192,049,992	R207,899,118	R224,135,860
PICO 1 Total Pharmaceutical Costs Maintaining SoC	R51,146,531	R51,146,531	R51,826,780	R52,516,076	R53,214,540	R53,922,293
PICO 1 Pharmaceutical NET Cost Difference	R0	-R274,028	-R555,346	-R844,098	-R1,140,432	-R1,444,500
PICO 2 Total Pharmaceutical Costs Rapid Uptake	R110,714,772	R108,553,738	R107,807,726	R107,022,669	R106,197,659	R105,331,772
PICO 2 Total Healthcare Costs Rapid Uptake	R49,840,000	R47,768,000	R46,303,757	R44,792,115	R43,232,073	R41,622,610
PICO 2 Total Pharmaceutical Costs Maintaining SoC	R110,714,772	R110,714,772	R112,187,278	R113,679,369	R115,191,305	R116,723,349
PICO 2 Pharmaceutical NET Cost Difference	R0	-R2,161,034	-R4,379,552	-R6,656,701	-R8,993,646	-R11,391,577
PICO 3 Total Pharmaceutical Costs Rapid Uptake	R40,894,033	R43,141,573	R45,992,788	R48,912,214	R51,901,161	R54,960,962
PICO 3 Total Healthcare Costs Rapid Uptake	R69,795,000	R65,649,600	R62,322,206	R58,894,690	R55,364,979	R51,730,959
PICO 3 Total Pharmaceutical Costs Maintaining SoC	40894032.6	40894032.6	41437923.23	41989047.61	42547501.95	43113383.72
PICO 3 Pharmaceutical NET Cost Difference	R0	R2,247,540	R4,554,865	R6,923,166	R9,353,659	R11,847,579
TOTAL PHARMACEUTICAL COST NET DIFFERENCE OVERALL	R0	-R187,523	-R380,033	-R577,632	-R780,419	-R988,498
Slow Adoption Scenario						
PICO 1 Total Pharmaceutical Costs Slow Uptake	51,146,531	51,009,517	51,549,107	52,094,027	52,644,324	53,200,043
PICO 1 Total Healthcare Costs Slow Uptake	148,707,000	21,259,800	43,085,111	65,487,214	88,477,592	112,067,930
PICO 1 Total Pharmaceutical Costs Maintaining SoC	51,146,531	51,146,531	51,826,780	52,516,076	53,214,540	53,922,293
PICO 1 Pharmaceutical NET Cost Difference	-	-R137,014	-R277,673	-R422,049	-R570,216	-R722,250
PICO 2 Total Pharmaceutical Costs Slow Uptake	110,714,772	109,634,255	109,997,502	110,351,019	110,694,482	111,027,561
PICO 2 Total Healthcare Costs Slow Uptake	49,840,000	48,804,000	48,403,314	47,983,338	47,543,627	47,083,733
PICO 2 Total Pharmaceutical Costs Maintaining SoC	110,714,772	110,714,772	112,187,278	113,679,369	115,191,305	116,723,349
PICO 2 Pharmaceutical NET Cost Difference	-	-R1,080,517	-R2,189,776	-R3,328,350	-R4,496,823	-R5,695,789
PICO 3 Total Pharmaceutical Costs Slow Uptake	40,894,033	42,017,803	43,715,356	45,450,631	47,224,332	49,037,173
PICO 3 Total Healthcare Costs Slow Uptake	69,795,000	67,722,300	66,522,740	65,279,292	63,991,001	62,656,894
PICO 3 Total Pharmaceutical Costs Maintaining SoC	40,894,033	40,894,033	41,437,923	41,989,048	42,547,502	43,113,384
PICO 3 Pharmaceutical NET Cost Difference	-	1,123,770	2,277,432	3,461,583	4,676,830	5,923,789
TOTAL PHARMACEUTICAL COST NET DIFFERENCE OVERALL	-	-R93,761	-R190,017	-R288,816	-R390,209	-R494,249

Sensitivity analyses

The variables for the sensitivity analysis included rates of PHC referral, hospitalisation and ICU admission rates, and severe asthma prevalence based on expert opinion. For SABA usage, the base case annual number of inhalers was derived from Western Cape utilisation data and the upper limit from CCMDD dispensing data from other Provinces. An upper sensitivity analysis was also applied for PICO 1 based on expert consensus. No additional sensitivity analysis was applied to medicine use for PICO 2 and 3 outside of SABA use for the standard of care, given the time constraints to conduct the BIAs. For general ward and ICU length of stay, base case values were derived from the study by Manyureke et al (Manyureke,2023) with upper and lower estimates informed by expert opinion. See Table 14. Univariate sensitivity analysis was applied to the hospitalisation rate for PICO 1, ICU admission rate for PICO 3, PICO 1 SABA, budesonide and beclometasone usage, PICO 2/3 SABA use and severe asthma adult rates. Multivariate sensitivity analysis was undertaken for emergency room, general ward and ICU costs accounting for uncertainty around general ward and ICU length of stay, and PHC referral rates to the emergency room.

Table 14: Variables for the sensitivity analysis

PICO	Variable	Lower limit	Base	Upper limit	Reference
1-3	PHC referrals	5%	10%	15%	Expert opinion
1	Hospitalisation	5%	10%	15%	Expert opinion
3	ICU admission rate	2%	3%	4%	Manyeruke, 2023; Salie, 2023, Expert opinion
1	Salbutamol; 100mcg; Inhaler; 200 Doses	-	2	4	Expert opinion
1	Budesonide; 200mcg; Inhaler; 300 Doses	-	2	4	Expert opinion
1	Beclometasone; 200mcg; Inhaler; 200 Doses	-	2	4	Expert opinion
1	Budesonide/Formoterol; 160/4.5 mcg, Inhaler; 60 Doses	-	3	6	Expert opinion
2-3	SABA usage	-	6	12	Western Cape CDU/pharmacy data; other Provinces CCMDD data
3	ICU LOS	1	3	5	Manyeruke, 2023; Expert opinion
1-3	GW LOS	1	2	3	Manyeruke, 2023; Expert opinion
3	Severe asthma prevalence	1	4	7	Expert opinion
1-3	PHC cost	429.72	411.13	475.28	Contract circulars HP07-2023DAI, HP09-2023SD, NDoH: UPFS 2024, Annexure A2; NDoH price on file for hydrocortisone 100mg/ml injection
1-3	ER costs w/ PHC referral (ZAR)	2157.50	2680.70	4355.30	HE ² RO costing data on file
1-3	GW cost & LOS (ZAR)	6953.80	14345.90	22198.20	HE ² RO costing data on file
3	GW + ICU cost & LOS (ZAR)	35017.50	101283.30	172635.60	HE ² RO costing data on file

CDU=Chronic Dispensary Unit, CCMDD=Central Chronic Medicines Dispensing and Distribution, ER=emergency room, GW=General ward, ICU=intensive care unit, LL=lower limit, LOS=length of hospitalisation stay, NDoH=National Department of Health, SABA=short-acting β_2 agonist, UL=upper limit, UPFS=Uniform Patient Fee Schedule, ZAR=South African Rand

Sensitivity analysis was undertaken for the various asthma severities, mild intermittent asthma (PICO 1), mild persistent asthma (PICO 2), and moderate asthma (PICO 3).

For tornado graphics below (PICO 1, 2, & 3), the expected value (EV) vertical line represents the expected total treatment cost (per individual patient) assuming all base case values for input parameters. The horizontal bars represent the variation in total treatment cost after applying the lower and upper estimates around input parameters.

PICO 1

The cost of treatment for mild intermittent asthma is primarily influenced by the number of inhalers used by individuals both for the standard of care or ICS/formoterol. Inappropriate use of inhalers could translate to a doubling in the cost of medication for both treatment arms.

Uncertainty around costs of PHC, ER and general ward admissions could affect the total treatment costs, but equally across both arms. Furthermore, uncertainty around the proportions of patients requiring further upward referrals to the hospital level may also increase costs. As needed ICS/formoterol is not more cost-effective than the current standard of care (ICS/SABA as needed) despite reduced medication costs, given that healthcare resource use is higher in the intervention arms due to additional PHC visits required to pick up inhalers. (Refer to the tornado diagram in Figure 5).

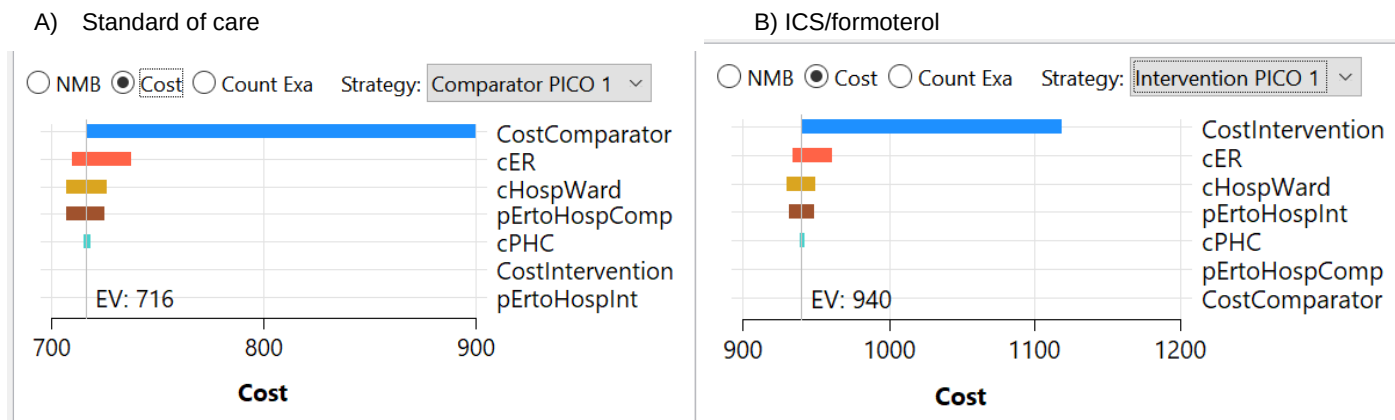


Figure 5: Tornado diagrams for A) Standard of care and B) ICS/formoterol for mild intermittent asthma (PICO 1)

Abbreviations: CostComparator =Annual per patient cost of standard of care; CostIntervention=Annual per patient cost of ICS/formoterol; cER=Cost of emergency room visit; CHospWard=Cost of stay in a general ward; cPHC=Cost of PHC care; pERtoHospComp=Probability of hospitalisation following Emergency room visit for standard of care; pERtoHospInt=Probability of hospitalisation following Emergency room visit for intervention; EV=expected value

PICO 2

For mild persistent asthma, the sensitivity analysis revealed that the budget impact of the new intervention is primarily influenced by the cost of the standard of care. Furthermore, variation in general ward admission costs, influenced by length of stay and uncertainty around the costs had a notable impact on the budget, while the costs of ER admission and PHC care had a smaller influence on budget impact. (Refer to the tornado diagram in Figure 6).

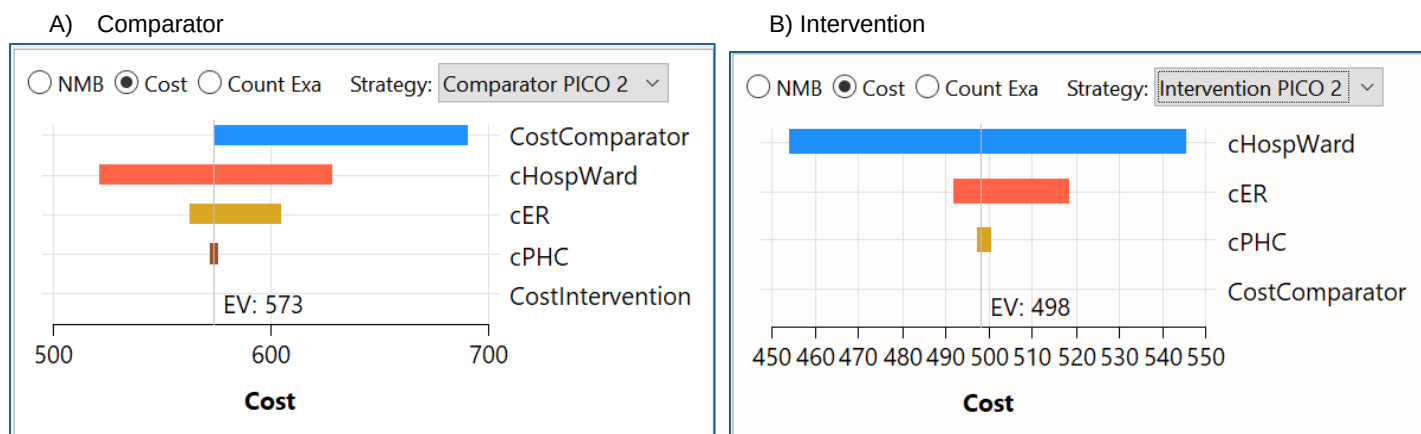


Figure 6: Tornado diagrams for comparator and intervention for mild persistent asthma (PICO 2)

Abbreviations: CostComparator =Annual per patient cost of standard of care; CostIntervention=Annual per patient cost of new intervention; cER=Cost of emergency room visit; CHospWard=Cost of stay in a general ward; cPHC=Cost of PHC care; EV=expected value

PICO 3

For moderate asthma, the sensitivity analysis highlighted that variation in general ward admission costs was a major driver of the budget impact, followed by variation in ICU and ER costs—although the impact of ICU costs was less pronounced due to the low proportion of patients requiring ICU admission. The cost of the standard of care may also be higher due to increased dispensing of SABA inhalers.

ICS/formoterol was cheaper than standard of care due to substantial reductions in exacerbations and hospitalisation despite higher treatment costs. (Refer to the tornado diagram in Figure 7).

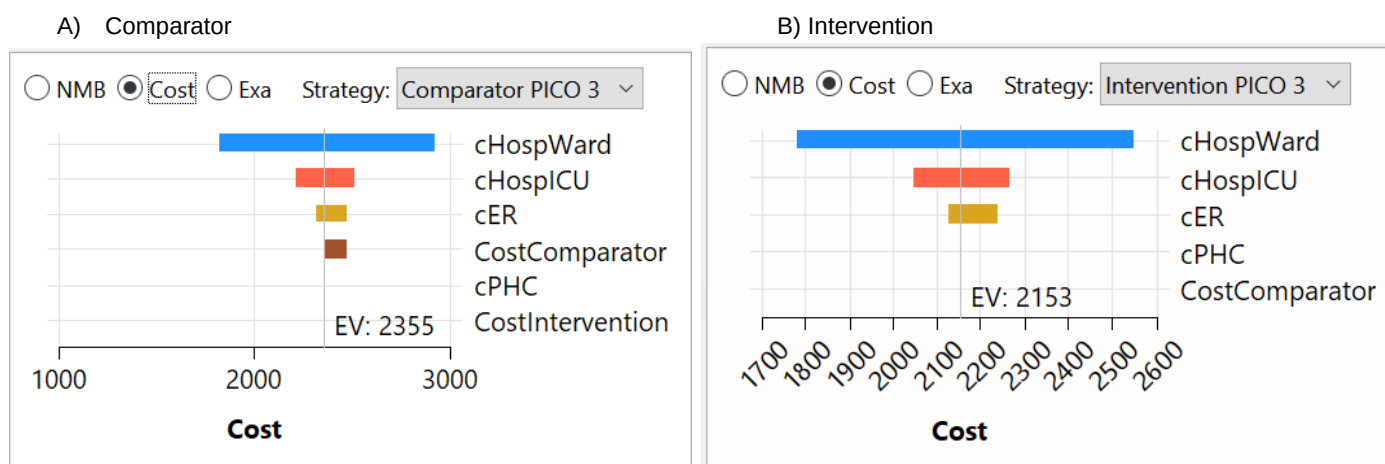


Figure 7: Tornado diagrams for comparator and intervention for moderate asthma (PICO 3)

Abbreviations: CostComparator =Annual per patient cost of standard of care; CostIntervention=Annual per patient cost of new intervention; CER=Cost of emergency room visit; CHospWard=Cost of stay in a general ward; cHospICU=Cost of intensive care unit stay; cPHC=Cost of PHC care; EV=expected value

PICO 3: Severe asthma prevalence

For the BIA model, the prevalence of severe asthma amongst adults in South Africa was informed by expert opinion. Thus, a sensitivity analysis was undertaken, varying the rate from 1% to 7%.

The base model demonstrated that pharmaceutical costs were higher in the ICS/formoterol group compared to standard of care, but this was offset by lower non-pharmaceutical costs (mostly hospitalisation).

The sensitivity analysis (Table 15) showed that uncertainty around the proportion of patients with severe asthma has a considerable impact on the total budget impact of managing asthma.

Table 15: Sensitivity analysis adjusting for prevalence of severe asthma among adults

Comparator vs Intervention:	Model	Full eligible population	Status quo	Year 1	Year 2	Year 3	Year 4	Year 5
Patient population that will receive the new technology	1000	1,806,000(629,000-2,983,000)	47,000(40,000-109,000)					
A: RAPID ADOPTION (20% per annum)								
Status quo implementation scenario (rapid)	100%	100%	100%	80%	60%	40%	20%	0%
Pharmaceutical costs	870,000	1,571,220,000 (547,230,000-2,595,210,000)	40,894,033 (34,800,000-94,830,000)	32,715,226 (27,840,000-75,864,000)	24,862,754 (21,157,704-57,654,743)	16,795,619 (14,292,734-38,947,701)	8,509,500 (7,241,414-19,732,853)	0(0, 0)
Healthcare resource use costs	1,485,000	2,681,910,000 (934,065,000-4,429,755,000)	69,795,000 (59,400,000-161,865,000)	55,836,000 (47,520,000-129,492,000)	42,433,964 (36,114,012-98,410,683)	28,665,557 (24,396,219-66,479,697)	14,523,405 (12,360,344-33,681,938)	0(0, 0)
Other costs/savings not captured elsewhere	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Total cost of current treatment pathway	2,355,000	4,253,284,955 (1,481,295,000-7,024,965,000)	110,689,033 (94,200,000-256,695,000)	88,551,226 (75,360,000-205,356,000)	67,296,718 (57,271,716-156,065,426)	45,461,176 (38,688,953-105,427,398)	23,032,905 (19,601,758-53,414,791)	0(0, 0)
Rapid adoption of new technology	100%	100%	100%	20%	40%	60%	80%	100%
Pharmaceutical costs	1,109,000	2,003,189,555 (697,561,000-3,308,147,000)	52,131,733 (44,360,000-120,881,000)	10,426,347 (8,872,000-24,176,200)	21,130,034 (17,979,995-48,995,487)	32,116,595 (27,328,694-74,470,690)	43,391,661 (36,922,887-100,614,867)	54,960,962 (46,767,452-127,441,306)
Healthcare resource use costs	1,044,000	1,885,464,000 (656,676,000-3,114,252,000)	49,068,000 (41,760,000-113,796,000)	9,813,600 (8,352,000-22,759,200)	19,888,242 (16,926,163-46,123,795)	30,229,133 (25,726,922-70,105,862)	40,841,574 (34,758,786-94,717,693)	51,730,959 (44,026,348-119,971,798)
Other costs/savings not captured elsewhere	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Total cost of current treatment pathway	2,153,000	3,888,653,555 (1,354,237,000-6,422,399,000)	101,199,733 (86,120,000-234,677,000)	20,239,947 (17,224,000-46,935,400)	41,018,276 (34,906,158-95,119,282)	62,345,728 (53,055,615-144,576,552)	84,233,235 (71,681,674-195,332,560)	106,691,921 (90,793,800-247,413,104)
NET BUDGET IMPACT (future - current treatment pathway costs)	[-202,000]	[-364,631,400 (-127,058,000-602,566,000)]	[-9,489,300 (-8,080,000; -22,018,000)]	108,791,173 (92,584,000-252,291,400)	108,314,994 (92,177,874-251,184,708)	107,806,904 (91,744,569-250,003,950)	107,266,140 (91,283,432-248,747,351)	106,691,921 (90,793,800-247,413,104)
B: SLOW ADOPTION (10% per annum)								
Status quo implementation scenario (slow)	100%	100%	100%	90%	80%	70%	60%	50%
Pharmaceutical costs	870,000	1,571,374,955 (547,230,000-2,595,210,000)	40,894,033 (34,800,000-94,830,000)	36,804,629 (31,320,000-85,347,000)	33,150,339 (28,210,272-76,872,991)	29,392,333 (25,012,285-68,158,477)	25,528,501 (21,724,242-59,198,558)	21,556,692 (18,344,312-49,988,249)
Healthcare resource use costs	1,485,000	2,681,910,000 (934,065,000-4,429,755,000)	69,795,000 (59,400,000-161,865,000)	62,815,500 (53,460,000-145,678,500)	56,578,619 (48,152,016-131,214,244)	50,164,725 (42,693,383-116,339,469)	43,570,214 (37,081,033-101,045,815)	36,791,415 (31,311,842-85,324,770)
Other costs/savings not captured elsewhere	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Total cost of current treatment pathway	2,355,000	4,253,130,000 (1,481,295,000-7,024,965,000)	110,689,033 (94,200,000-256,695,000)	99,620,129 (84,780,000-231,025,500)	89,728,957 (76,362,288-208,087,235)	79,557,058 (67,705,668-184,497,946)	69,098,715 (58,805,274-160,244,373)	58,348,106 (49,656,154-135,313,019)
Slow adoption of new technology	100%	100%	100%	10%	20%	30%	40%	50%
Pharmaceutical costs	1,109,000	2,003,189,555 (697,561,000-3,308,147,000)	52,131,733 (44,360,000-120,881,000)	5,213,173 (4,436,000-12,088,100)	10,565,017 (8,989,998-24,497,743)	16,058,297 (13,664,347-37,235,345)	21,695,830 (18,461,444-50,307,434)	27,480,481 (23,383,726-63,720,653)
Healthcare resource use costs	1,044,000	1,885,464,000 (656,676,000-3,114,252,000)	49,068,000 (41,760,000-113,796,000)	4,906,800 (4,176,000-11,379,600)	9,944,121 (8,463,082-23,061,897)	15,114,567 (12,863,461-35,052,931)	20,420,787 (17,379,393-47,358,846)	25,865,479 (22,013,174-59,985,899)
Other costs/savings not captured elsewhere	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Total cost of current treatment pathway	2,153,000	3,888,653,555 (1,354,337,000-6,422,399,000)	101,199,733 (86,120,000-234,677,000)	10,119,973 (8,612,000-23,467,700)	20,509,138 (17,453,079-47,559,641)	31,172,864 (26,527,808-72,288,276)	42,116,617 (35,840,837-97,666,280)	53,345,961 (45,396,900-123,706,552)
NET BUDGET IMPACT (future - current treatment pathway costs)	[-202,000]	[-364,631,400 (-127,058,000 - 602,566,000)]	-9,489,300 (-8,080,000, -22,018,000)	109,740,103 (93,392,000-254,493,200)	110,238,095 (93,815,367-255,646,876)	110,729,922 (94,233,476-256,786,222)	111,215,332 (94,646,111-257,910,653)	111,694,067 (95,053,054-259,019,571)

Threshold price

A threshold price analysis was conducted to determine the maximum price at which budesonide/formoterol 160/4.5 mcg (60 doses) would be cost-neutral relative to current standard care, from a public payer perspective. The aim was to support government tender negotiations by identifying break-even prices that would result in no net increase in total treatment costs, after accounting for both medication and healthcare use.

Methodological approach

1. Total per-patient treatment costs were estimated for both ICS/formoterol and standard of care regimens. This included medication prices and healthcare resource use (e.g., outpatient visits, emergency care, hospitalisations), which were adjusted based on expected reductions from improved asthma control under ICS/formoterol.
2. For PICO 3, a weighted average cost of the ICS/formoterol was calculated to reflect the mixed use of both budesonide/formoterol 160/4.5 mcg and 320/9 mcg formulations, based on the assumption that 39.5% of patients would require the higher-dose strategy. The percentage of 39.5% was derived from National Surveillance data used in the status quo and BIA models.
3. The price of each ICS/formoterol inhaler was then iteratively adjusted until the total average cost per patient matched that of the current standard of care, identifying the threshold (break-even) price at which the new regimen would be cost-neutral.

Findings

- Across all three scenarios, the threshold (cost-neutral) price for budesonide/formoterol 160/4.5 mcg (60 doses) was estimated at R50.54.
- In PICO 3, the price threshold for budesonide/formoterol 320/9 mcg (60 doses) was estimated at R109.25.

By explicitly incorporating realistic patient proportions and dosing strategies across the three scenarios, this analysis supports transparent and evidence-based procurement decisions aligned with national health priorities.

Discussion

For PICO 1 and 2, medicine costs are lower for ICS/formoterol than standard of care, whilst healthcare resource costs lower for PICO 2 and 3. For PICO 2, both medicine and health care utilisation costs are lower for ICS/formoterol, resulting in overall savings to the public health sector. For PICO 3, the higher medicine costs are offset by lower healthcare utilisation costs, resulting in an overall lower cost of treatment. Implementing new asthma management guidelines at scale does however require investments in procurement, health provider training, and patient education to ensure adherence.

Sensitivity analyses indicate uncertainty surrounding the costs of emergency room visits, hospitalisations and ICU admissions, as well as the proportion of people referred from PHC for hospitalisation. There is further uncertainty around the utilisation patterns of medicines for the standard of care, which may result in higher treatment costs. Furthermore, there is high uncertainty around the prevalence of adults with severe asthma, which could significantly impact the total budget impact for managing asthma. Overall, local epidemiological data for asthma are very limited. Engaging in price monitoring or negotiations could maintain or lower the price of budesonide/formoterol inhalers, respectively. Comprehensive diagnostic work-up of asthma, rational prescribing and use of asthma medications and patient adherence may improve the t access to budesonide/formoterol inhalers and ultimately result in improved patient outcomes.

A budget impact analysis conducted in Egypt over 3 years showed that as-needed budesonide/formoterol amongst mild persistent asthma was a budget-saving option compared to low-dose ICS controller therapy with as-needed SABA, from the economic perspective of the payer (Health Insurance Organization) and patient (Elsisi, 2019). Conversely, two economic analyses conducted in Southeast Asia (Aggarwal, 2022; Bunupuradah 2021) comparing total direct treatment costs of standard of care (fluticasone/salmeterol controller therapy with as-needed SABA) to budesonide/formoterol MART amongst those with moderate asthma, from a health payer's perspective, estimated that standard of care cost was lower than MART primarily due to lower medication costs. These analyses provide a platform for funders to negotiate lower prices with pharmaceutical suppliers for ICS/formoterol.

Strengths

This budget impact analysis offers a robust and comprehensive evaluation of the economic implications of implementing ICS/formoterol for the treatment of asthma. Several methodological strengths ensure the reliability and relevance of the findings for local healthcare decision-making.

Rigorous triangulation of prevalence estimates was undertaken. The analysis estimated prevalence from a diverse range of sources, including published studies, local utilisation patterns, and asthma inhaler dispensing data. Furthermore, expert opinion was systematically integrated to refine these estimates, ensuring that the estimates reflect the best possible local prevalence of asthma disaggregated by severity. This approach accounts for the variations in asthma severity distribution and provides a nuanced understanding of the target population.

Both pharmaceutical and non-pharmaceutical health resource costs were included in the BIA models. We accounted for direct pharmaceutical costs and estimated health resource utilisation costs, such as emergency visits and hospitalisations. Health resource costs were derived using Markov modelling, which employed inputs from a meta-analysis of data from the PICO 1, 2 and 3 systematic reviews of available clinical trials. This ensures that the cost estimates are based on high-quality, evidence-based data.

Local contextualisation was considered ensuring that the analysis aligns global evidence with local data, ensuring its relevance for decision-makers. Adjustments for local pricing, healthcare resource availability, and patient demographics enhance its applicability to the South African public healthcare setting.

Economic evidence to support evidence-based policy decisions was provided, and the comprehensive approach provides policymakers with actionable insights to evaluate the economic feasibility of implementing new treatment regimens. It balances cost considerations with potential health system savings and patient outcomes. However, to account for uncertainty in the input parameters, the BIA model incorporated both univariate and multivariate sensitivity analyses. By varying key cost drivers individually and in combination, the analysis provided a robust understanding of how parameter uncertainty may influence outcomes. This approach ensures that decision-makers are equipped with insights into the range of possible budgetary impacts under different scenarios, enhancing confidence in the results.

Lastly, a threshold price was estimated to identify the price point at which the cost of the new treatment regimen would result in net zero budget impact compared to the current standard of care.

Limitations

Several limitations should be noted when interpreting the findings of the BIA research, primarily due to the poor quality or lack of local epidemiological data regarding South African adolescent and adults with asthma and COPD populations.

This includes limited data on the prevalence of intermittent, mild to moderate, and severe asthma, ICU and hospital admission rates for severe asthma, emergency room treatments, and the current use of relievers in those with intermittent, moderate, and severe asthma within this demographic. The available published data on asthma prevalence are inconsistent, using varying definitions and study methodologies, highlighting the need for global standardised definitions, methodologies and denominators.

For COPD, the GOLD guidelines were used to indirectly estimate utilisation rates of ICS/LABA used by COPD patients.

Proxies were calculated using national surveillance data to proportion coverage of inhalers to the different sub-populations.

National procurement surveillance data suggest that SABA inhalers may be used irrationally in practice, a factor that has not been included in the BIA model. Furthermore, published literature documents the underdiagnosis of asthma, particularly among adolescents with severe asthma.

For practical purposes, a linear model was used for the BIA, rather than a Markov model, considering the "step-up" and "step-down" probabilities over adolescent/adults' lifetimes. To estimate coverage over five years, only annual population growth was considered, without considering any potential increase in eligible population coverage through programmatic improvements.

To address uncertainties, sensitivity analyses were performed where applicable; however, these were not conducted on efficacy estimates related to treatment. Additionally, there is a paucity of data directly comparing the efficacy and safety of ICS/SABA to ICS/formoterol for mild intermittent asthma, and although expert opinion suggests that these agents are comparable in this clinical setting, further research is required to determine the effects.

Most of the ICS/formoterol studies were based on dry powder inhalations (DPI) rather than aerosol-metered dose devices (MDI). Pragmatic considerations for the DPI include ease of patient use and possibly reduced environmental impact compared to the MDI (Refer to the rapid evidence review for PICO 1).

Conclusion

The budget impact analysis demonstrates that adopting ICS/formoterol treatment strategies for asthma, has the potential to yield cost savings for the South African public health sector. Across the different PICO scenarios, the reduction in healthcare utilisation costs (primarily from fewer hospitalisations, emergency visits, and ICU admissions) and the lower medicine costs for PICOs 1 and 2 lead to net savings. The higher medicine costs for the intervention group in PICO 3 are also offset by the lower healthcare utilisation costs, due to improved patient outcomes.

Key factors influencing the budget impact include the price of budesonide/formoterol inhalers, the prevalence of asthma, the relative population cohorts based on disease severity, and uncertainties surrounding healthcare utilisation patterns. While the analysis highlights potential economic benefits, successful implementation of revised asthma guidelines requires additional investments in procurement, health provider training, and patient education to ensure adherence and optimal treatment outcomes. Given the limited availability of local epidemiological data, further research is needed to refine cost estimates and validate assumptions. Policymakers may also consider engaging in price monitoring and negotiations for budesonide/formoterol inhalers to enhance affordability and sustainability. By aligning treatment strategies with cost-effective interventions, the health system can improve asthma management, while optimising resource allocation.

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Appendices

Appendix A: Prevalence studies

Supplementary Table 1: Summary of prevalence studies

S African prevalence rates	Children				Adolescents				Adults			
	Age (yrs)	P	Definition	Refs	Age (yrs)	P	Definition	Refs	Age (yrs)	P	Definition	Refs
Overall asthma	6-7	11.2%	Questionnaire Parent/guardian surveyed: Has your child had wheezing or whistling in the chest in past 12 months.	Polokwane, ISAAC 3 (2007) [1]	13-14	16.0%	Questionnaire: Current asthma symptoms: Have you (your child) had wheezing or whistling in the chest in the past 12 months.	Cape Town, ISAAC 1 (1995)[2]	18-45	14.4%	Wheezing symptoms: During the last 12 months have you experienced attacks of wheezing or whistling breath?"	South Africa, WHS (2003) [5]
					13-14	20.3%	Questionnaire: Current asthma symptoms: Have you (your child) had wheezing or whistling in the chest in the past 12 months.	Cape Town, ISAAC 3 (2002)[2]	18-45	6.09%	Clinical asthma: doctor-diagnosed asthma and/or a positive response in either of 2 questions "Have you ever been treated for asthma" or "Have you been taking any medications or treatment for asthma during the last 2 weeks?"	South Africa, WHS (2003) [5]
					13-14	18.0%	Questionnaire: Current asthma symptoms: Have you (your child) had wheezing or whistling in the chest in the past 12 months.	Polokwane, ISAAC 3 (2007) [1]	18-45	5.92%	Doctor diagnosed asthma	South Africa, WHS (2003) [5]
					13-14	21.3%	Questionnaire: Current asthma symptoms: Have you (your child) had wheezing or whistling in the chest in the past 12 months.	Cape Town, GAN Phase 1 (2017) [3]	Adults	6-10%	Data on adults in SA are less reliable but the estimated prevalence of asthma 6-10% and rising	South Africa, Zar (2013) [6]
					13-14	13.1%	Diagnosis of asthma ever	Cape Town, ISAAC 1 (1995) [2]	5-69	13.2% (10.5-16.5)	Self-reported current wheezing	African region, SR (2022) [7]
					13-14	14.4%	Diagnosis of asthma ever	Cape Town, ISAAC 3 (2002) [2]	5-69	11.3% (9.0-14.1)	Diagnosis of asthma ever (by a physician)	African region, SR (2022) [7]
					13-14	16.6%	Diagnosis of asthma ever	Cape Town, GAN Phase 1 (2017) [3]	≥15	3.5% (3.1-4.0)	DHS 2016 + self-reported past diagnosis by healthcare worker	South Africa, modelled-based study (2024) [8]
					13-14	13.7%	Questionnaire: Current asthma symptoms: Have you (your child) had wheezing or whistling	Durban/Richards Bay (2021) [4]				

							in the chest in the past 12 months.					
					13-14	12.9 %	Diagnosis of asthma ever	Durban/ Richards Bay (2021) [4]				
Severe asthma	6-7	5.7 %	Questionnaire Parent/guardian surveyed: severe wheeze if ≥ 2 of ffg: (1) ≥ 4 attacks in the last 12 months; (2) speech disturbance in the last 12 months; (3) > 1 night of sleep disturbance in the last 12 months; (4) wheezing with exercise in the last 12 months	Polokwane, ISAAC 3 (2007) [1]	13-14	7.3 %	Questionnaire: following symptoms in last 12 months: 1) ≥ 4 attacks of wheezing, 2) sleep disturbed due to wheezing ≥ 1 night a week, 3) wheezing severe enough to limit speech	Cape Town, ISAAC 1 (1995) [2] [9]	Adults	3.6 % (3-4.1)	Questionnaire: participants identified from pharmacy databases & surveyed Definition of severe asthma	Netherlands, questionnaire of diagnosed asthmatics (2011) [10]
					13-14	9.5 %	Questionnaire: following symptoms in last 12 months: 1) ≥ 4 attacks of wheezing, 2) sleep disturbed due to wheezing ≥ 1 night a week, 3) wheezing severe enough to limit speech	Cape Town, ISAAC 3 (2002) [2] [9]	Adults	8.1 %	Utilisation data: Nationwide prescription database	Denmark, prescription database (2010) [11]
					13-14	11.8 %	Questionnaire: following symptoms in last 12 months: 1) ≥ 4 attacks of wheezing, 2) sleep disturbed due to wheezing ≥ 1 night a week, 3) wheezing severe enough to limit speech	Cape Town, GAN Phase 1 (2017) [3] [9]	Children & adults	5-10%	"Little is understood regarding the prevalence of severe asthma in adults or children, especially when using rigorous definitions as outlined here. However, figures of 5–10% of the total asthma population are often estimated".	Global (2014) [12]
					13-14	9.1 %	Questionnaire: following symptoms in last 12 months: 1) ≥ 4 attacks of wheezing, 2) sleep disturbed due to wheezing ≥ 1 night a week, 3) wheezing severe enough to limit speech	Durban/ Richards Bay (2021) [4]	13-36	25.60%	Severe asthma was defined by pulmonologist(s) as asthma that required treatment with guideline-suggested medications for GINA step 4-5 asthma (high-dose ICS and long-acting β -agonist or leukotriene modifier/theophylline) for the previous year or systemic corticosteroid therapy for $> .50\%$ of the previous year to prevent it from becoming uncontrolled, or disease that remained uncontrolled despite this therapy. Uncontrolled asthma was defined as consistently having an ACQ score of ≥ 1.5	East Africa (Uganda, Kenya, Ethiopia), prospective cohort study (2023) [18]
					13-15	3.7 %	Diagnosis of severe asthma with reported severe asthma symptoms	Durban/ Richards Bay (2021) [4]	≥ 17	7.80 %	Patients with severe asthma were defined as patients prescribed 1600 mg per day	Japan, health insurance

								budesonide equivalent dosage or a greater ICS dosage plus at least one controller (LABA, leukotriene receptor antagonist (LTRA), or theophylline) during 12 months before the index date. The budesonide equivalent dosage of ICS was calculated based on the prescriptions before the index date. Patients with 183 or more prescription days for systemic corticosteroids within 12 months before the index date were also defined as patients with severe asthma.	claims database (2017) [19]
		Children & adults	5-10 %	"Little is understood regarding the prevalence of severe asthma in adults or children, especially when using rigorous definitions as outlined here. However, figures of 5–10% of the total asthma population are often estimated"	Global (2014) [12]	≥18	21.70%	Difficult-to-treat or severe asthma was defined by poor symptom control, exacerbations and/or oral corticosteroid/biologic use despite medium/high-dose inhaled therapy.	Australia, cross-sectional survey (2021) [20]
COPD	n/a			n/a		Adults	8.0 % (6.2 - 10.2)	Population-based studies & modelling systematic review using the GOLD & LLN definitions of COPD	South Africa, SR & modelling based on BOLD study (2019) [13] [17]
						Adults	8% (6-11)	Systematic review of published literature, conference proceedings.	SSA, SR & MA (2020) [14]
						Adults	22%	Nkhoma 2023: In Africa, COPD has a prevalence rate of around 20% in South Africa, cited the BOLD study; Buist 2007 (BOLD study): Cape Town site COPD prevalence of 22% using patient questionnaires.	Cape Town, prevalence survey (BOLD study) cited (2007) [16][17]
						≥15	1.8 % (1.5 - 2.2)	DHS 2016 + self-reported symptoms suggestive of the condition Note: Association between asthma and COPD: OR 14.6 (10.3-19.9)	South Africa, modelled-based study (2024) [8]
						COPD Group E	26.7 %	The GOLD ABCD classification was changed to ABE in 2023 such that Groups C and D are now grouped together and termed Group E. In the COPDGene cohort, GpA=37.0%; GpB=26.7%; GpC=22.3%; GpD=22.3% (i.e. GpE= GpC+GpD=26.7%) [22]; COPD Gold GpE are COPD patients with acute eosinophilic exacerbation with blood eosinophils ≥300/μL [21] [22] Studies suggest that the age-onset of COPD is ≥40 years [17][24]	USA, cross-sectional & longitudinal data from the Genetic Epidemiology of COPD Study (2010); associations of GOLD 2011 vs 2017 classifications [23]

Abbreviations: COPD=chronic obstructive pulmonary disease; P=prevalence, SR=systematic review

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Appendix B: Dispensing data (Western Cape)

Supplementary Table 2: Western Cape dispensing data of inhaled corticosteroid inhalers from 1 July 2023 to 30 June 2024

Age group	Datasource	Drugname	Formulation	Strength (mcg)	Doses per inhaler	Number of dispensings	Number of distinct patients issued to	Pack Size	Packs Issued
>40 yr	CDU	budesonide	Inhaler	200	300	11208	11191	1	12899
	JAC	beclometasone	Inhaler	200	200	31984	30406	1	72136
	JAC	budesonide	Inhaler	200	300	15369	15204	1	21857
>15 yr	CDU	budesonide	Inhaler	200	300	12503	12484	1	14328
	JAC	beclometasone	Inhaler	200	200	39631	37670	1	87885
	JAC	budesonide	Inhaler	200	300	18658	18458	1	26440
12-14yr	CDU	budesonide	Inhaler	200	300	143	143	1	144
	JAC	beclometasone	Inhaler	200	200	675	630	1	1250
	JAC	budesonide	Inhaler	200	300	269	268	1	365
Average packs per annum				Number of distinct patients issued to		Packs Issued	Average packs issues/patient/ annum	Rounded up	
Beclomethasone 200mcg inhaler, 200 doses				68706		161271	2.35	3	
Budesonide 200mcg inhaler, 300 doses				57748		76033	1.32	2	

Note: A CDU patient may receive at least one dispensing from the facility when the repeat prescription is issued.

Thus, assumed that 4 x beclomethasone inhalers (200 dose) and 3 x budesonide inhalers (300 dose) dispensed per patient per annum.

Abbreviations: CDU=Chronic Dispensing Unit; JAC=Pharmacy management system; mcg=microgram

Supplementary Table 3: Estimated number of inhalers per annum for PICO 1 (mild intermittent asthma)

	Medicine (Inhaler)	Doses/ inhalations	Dosing	Modelled Inhalers	Annual doses	Wastage accounted
Comparator	Beclometasone; 200mcg; Inhaler	200	1 inhalation as required	2	180	Unknown
	Budesonide; 200mcg; Inhaler	300	1 inhalation as required	2	180	Unknown
	Salbutamol; 100mcg; Inhaler	200	2 inhalations as required	2	360	Unknown
Intervention	Budesonide, Formoterol; 160mcg, 4.5mcg; Inhaler	60	1 inhalation as required	3	180	Unknown

*Wastage cannot be accurately estimated as treatment is used intermittently as needed. Furthermore, SABA/ICS is not available as a fixed-dose combination formulation and thus one ICS and one SABA are assumed to be dispensed per prescription. The number of modelled inhalers was guided by expert opinion.

Supplementary Table 4: Estimated number of inhalers per annum for PICO 2 ("mild" persistent asthma)

	Medicine (Inhaler)	Doses/ inhalations	Daily mcg dosing*	Annual doses/ inhalations	Annual Inhalers	Modelled Inhalers	Wastage
Comparator	Beclometasone; 200mcg; Inhaler	200	275	495	2.48	4	38%
	Budesonide; 200mcg; Inhaler	300	275	495	1.65	3	45%
	Salbutamol; 100mcg; Inhaler	200	0.48	720	3.60	6	40%
Intervention	Budesonide, Formoterol; 160mcg, 4.5mcg; Inhaler	60	108	243	4.06	6	32%

*From Hatter et al, assuming beclometasone is equivalent to budesonide and verified by Western Cape Central Dispensing Unit utilisation data of ICS over 12 months – see Table 6, below.

Supplementary Table 5: Estimated number of inhalers per annum for PICO 3 moderate asthma)

	Medicine (Inhaler)	Doses	Daily mcg dosing	Annual doses/ inhalations	Annual Inhalers	Modelled Inhalers	Wastage
Comparator	Budesonide, Formoterol; 160mcg, 4.5mcg; Inhaler	60	320/9 mcg	720	12	12	0%
	Budesonide, Formoterol; 320mcg, 9mcg; Inhaler	60	640/18 mcg	720	12	12	0%
	Salbutamol; 100mcg; Inhaler	200	200 mcg	720	3.6	6	40%
Intervention*	A: Budesonide, Formoterol; 160mcg, 4.5mcg; Inhaler	60	320/9 mcg	720	12	12	0%
	A: Budesonide, Formoterol; 160mcg, 4.5mcg; Inhaler	60	320/9 mcg	360	6	6	0%
	B: Budesonide, Formoterol; 320mcg, 9mcg; Inhaler	60	640/18 mcg	720	12	12	0%
	B: Budesonide, Formoterol; 160mcg, 4.5mcg; Inhaler	60	320/9 mcg	360	6	6	0%

*The intervention may be either:

A) Budesonide/ formoterol 160/4.5mcg 12 hourly as controller therapy with 160/4.5 mcg as needed for symptomatic relief: or

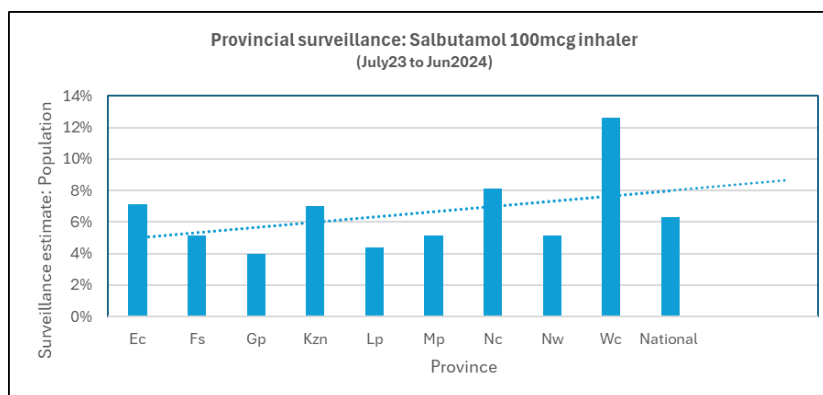
B) Budesonide/formoterol 320/9 mcg 12 hourly as controller therapy with 160/4.5 mcg as needed for symptomatic relief.

Appendix C: Comparative analysis of the different utilisation data sets

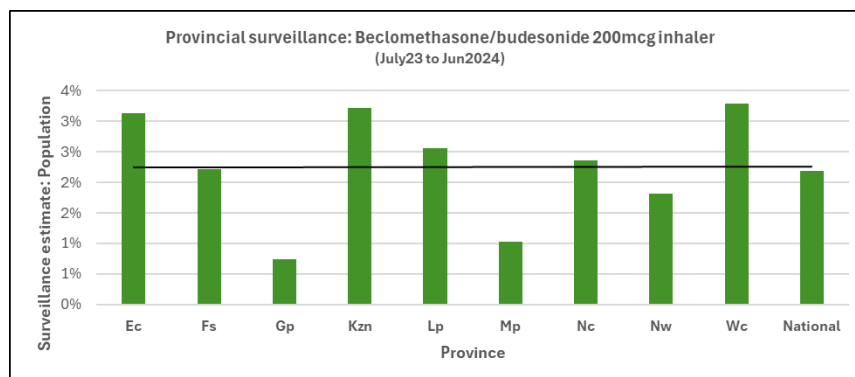
Supplementary Table 6: Uptake rates for the status quo scenario, comparing treatment access to asthma prevalence rates

	PICO 3 (adolescents)			PICO 3 (adults)		
	Uptake rate for status quo					
Prevalence estimate	8%	10%	6%	4%	5%	3%
Tender estimate	39.13%	31.30%	52.17%	14.30%	11.41%	19.09%
National surveillance data	99.68%	79.74%	132.90%	26.92%	21.51%	35.93%
WC Province surveillance data	2.01%	1.64%	2.61%	13.08%	10.42%	17.48%
WC Dispensing (CDU & Pharmacy)	0.64%	0.51%	0.85%	17.83%	14.19%	23.85%
	PICO 2 (adolescents)			PICO 2 (adults)		
	Uptake rate for status quo					
Prevalence estimate	22%	27%	17%	10%	14%	6%
Tender estimate	44.48%	36.24%	57.56%	44.48%	31.77%	74.13%
National surveillance data	38.85%	31.66%	50.28%	38.85%	27.75%	64.76%
WC Province surveillance data	6.50%	5.30%	8.41%	6.50%	4.64%	10.83%
WC Dispensing (CDU & Pharmacy)	0.83%	0.67%	1.07%	5.62%	4.01%	9.37%
	PICO 1 (adolescents)			PICO 1 (adults)		
	Uptake rate for status quo					
Prevalence estimate	22%	27%	17%	10%	14%	6%
Tender estimate	20.96%	17.08%	27.13%	62.26%	44.29%	104.05%
National surveillance data	1.91%	1.56%	2.48%	45.21%	32.16%	75.55%
WC Province surveillance data	4.48%	3.65%	5.80%	7.25%	5.16%	12.11%
WC Dispensing (CDU & Pharmacy)	0.95%	0.78%	1.23%	11.45%	8.15%	19.14%

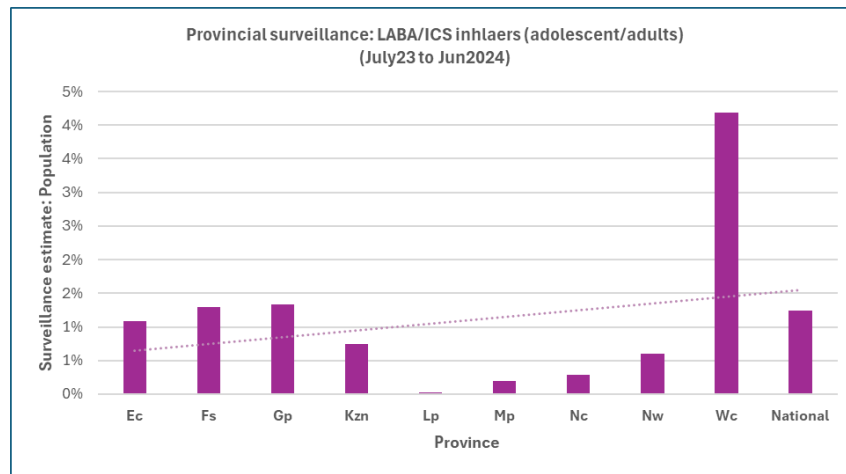
To better understand the variable data, a comprehensive analysis of the provincial surveillance data relative to the provincial population was conducted.



Supplementary Figure 1: Salbutamol 100mcg inhaler - Surveillance data: Population estimate

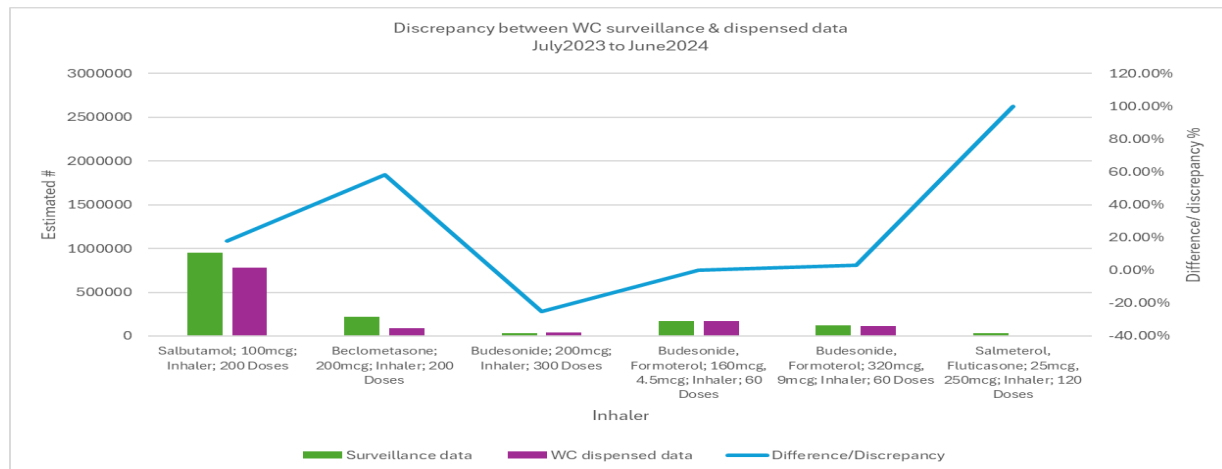


Supplementary Figure 2: Inhaled corticosteroid - Surveillance data: Population estimate



Supplementary Figure 3: ICS/LABA - Surveillance data: Population estimate

Supplementary Figures 2 to 4 show that Western Cape is an outlier, except for provincial surveillance data on budesonide/ beclomethasone 200mcg inhalers. This may suggest a higher prevalence of asthma or better clinical management of adolescent/ adult asthmatics. A comparison of procurement data with actual dispensed data revealed discrepancies regarding inhaled corticosteroids (budesonide and beclomethasone 200mcg inhalers). Notably, the 2020 edition of the PHC STGs and EML recommends ICS/LABA inhalers as doctor-initiated, with continued prescribing by nurse practitioners. Furthermore, Supplementary Figure 1 does not differentiate between acute, in-patient, outpatient, and chronic use of salbutamol inhalers due to limited data.



Supplementary Figure 4: Discrepancy between WC surveillance and dispensed data

It seems reasonable to base the status quo uptake rates on national surveillance data while applying sensitivity analyses to address any uncertainties.

The limitations of the model used to determine the status quo uptake rates include:

- A linear static model was used, which did not consider the "step-up" and "step-down" probabilities over the lifetime of adolescent/adult asthmatics.
- Asthma prevalence rates in South Africa are limited, including for different asthma "severities" and age groups.
- Frequent reports of underdiagnosis, particularly among adolescents with severe asthma, which may inflate ICS inhaler uptake rates beyond modelled expectations, and ICS/LABA inhaler uptake rates may fall below modelled expectations.
- Implementation of guideline changes typically takes 2-3 years, a factor to consider in forecasting.
- The model does not reflect inhaler use for acute exacerbations in healthcare facilities, or potential wastage.

Appendix D: Estimated doses/ inhalations for as-needed β 2-agonist reliever therapy

Supplementary table 7: Difference in number of as-needed β 2-agonist reliever inhalations used per day between ICS/FABA compared to standard of care.

Research question	RCTs (n)	Estimate for intervention versus control
PICO 1	N/A	Assumed that there is no difference based on expert opinion*
PICO 2	4 (7290)	Mean difference: 0.08, 95% CI 0.05 to 0.10), I^2 94.2
PICO 3	7 (15175)	Mean $\pm$ SD: 0.90 $\pm$ 0.26 vs 0.99 $\pm$ 0.24

*There are no available RCTs comparing ICS/SABA to ICS/FABA for mild intermittent adolescent/adult asthmatics

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