# Direct healthcare cost comparison of fluticasone/salmeterol and budesonide/formoterol maintenance and reliever therapy for moderate to severe asthma in the South African public sector

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**Background.** Moderate to severe asthma poses significant health and economic challenges in South Africa (SA), with varying asthma treatment costs. Inhaled corticosteroids/long-acting beta-2-agonists remain the cornerstone of asthma management. However, cost comparisons between fluticasone/salmeterol (FP/salm) and budesonide/formoterol (bud/form) as maintenance and reliever therapy (MART) are limited in low- and middle-income settings.
**Objective.** To compare the direct treatment costs of regular FP/salm plus as-needed short-acting beta-2-agonist (SABA) with bud/form MART in the SA public sector.
**Methods.** A comparative cost analysis was conducted from the SA public health sector perspective. Costs from the National Department of Health pharmaceutical tender and Uniform Patient Fee Schedule, and clinical effectiveness data on severe exacerbations avoided from three randomised controlled trials (AHEAD, COMPASS, COSMOS), informed annual per-patient costs. Univariate sensitivity analyses assessed the robustness of the findings.
**Results.** Annual direct per-patient treatment costs for bud/form MART were probably comparable to FP/salm plus as-needed SABA in COMPASS and COSMOS (USD145.84 and USD157.81). In the AHEAD study, a higher-dose bud/form MART regimen was more expensive (USD149.14 v. USD122.65). On average across studies, FP/salm was 0.58% less expensive. Medication costs were the primary cost driver, with variation in bud/form 160/4.5 µg pricing significantly influencing overall cost outcomes.
**Conclusion.** In SA's public sector, FP/salm plus as-needed SABA is comparable to bud/form MART for moderate to severe asthma in terms of cost. Bud/form's price sensitivity suggests potential for improved procurement. Future research should integrate real-world data, include indirect costs, and assess full-spectrum asthma management to inform efficient, equitable policy and evaluate economic impact.

**Keywords.** Asthma, budesonide/formoterol maintenance and reliever therapy, MART, ICS/LABA, comparative cost analysis, South Africa.

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**Study synopsis**
**What this study adds.** This study compares the direct costs of fluticasone/salmeterol (FP/salm) plus as-needed short-acting beta-2-agonist (SABA) v. budesonide/formoterol (bud/form) maintenance and reliever therapy (MART) for moderate to severe asthma, using South African (SA) public sector data. Findings address an evidence gap for cost-effective asthma care in low- to middle-income countries, where high mortality and SABA overuse require urgent, context-specific treatment optimisation.
**Implications of the findings.** The research findings suggest that currently bud/form MART is comparably priced to standard care with FP/salm plus as-needed SABA in SA's public sector. Bud/form's price sensitivity presents opportunities for strategic procurement. However, further comprehensive real-world economic evaluations across all asthma severities remain essential to guide evidence-informed, context-specific policy decisions.

Asthma is a major global health concern, affecting ~262 million people and causing 455 000 deaths in 2019.[1] In South Africa (SA), asthma prevalence rates are uncertain owing to limited epidemiological data. However, the Global Burden of Disease 2021 study reported a burden of 331.3 disability-adjusted life-years per 100 000 people (95% uncertainty interval (UI) 293.76 - 375.8) and a mortality rate of 9.09 deaths per 100 000 (95% UI 8.13 - 10.19).[2] While mortality has declined over time, SA ranked third globally in asthma-related deaths in 2018.[3]

While international guidelines recommend anti-inflammatory reliever inhaled corticosteroid (ICS)-containing therapy as a cornerstone

of asthma management – owing to the proven efficacy of ICS in reducing airway inflammation, severe exacerbations, hospitalisations, mortality, and inappropriate short-acting beta-2-agonist (SABA) use – the uptake of ICS-based therapies remains limited in many low- to middle-income settings owing to cost and availability constraints. For moderate to severe asthma, recommended options include either regular maintenance ICS/long-acting beta-2-agonist (LABA) therapy plus as-needed SABA, or maintenance and reliever therapy (MART) using ICS-formoterol combinations.[4] The efficacy and safety of fluticasone propionate/salmeterol (FP/salm) and MART in controlling moderate to severe asthma and reducing severe asthma exacerbations have been well reported in published literature.[5]

The economic burden of moderate to severe asthma is significant, varying between settings and including direct healthcare costs (e.g. medications, hospitalisations) and indirect costs (e.g. productivity losses, premature mortality).[3] While cost-effectiveness studies of FP/salm and MART were primarily conducted in high–income countries,[6-10] recent comparative cost analyses from upper and lower middle-income countries (Thailand, Indonesia and Vietnam) suggest that twice-daily FP/salm maintenance therapy is associated with lower total direct costs compared with budesonide/formoterol (bud/form) MART.[11,12]

SA's inequitable health system features are marked by disparities, with a well-resourced private sector serving 16% of the population and an underfunded, overburdened public sector for the majority.[13] In the public sector, centralised tender procurement secures lower medicine prices through bulk purchasing, while the private sector operates under the Single Exit Price regulation, which often results in significantly higher medicine costs. As the country progresses towards Universal Health Coverage, harmonising policies, pricing, and reforming the overall health system will be essential. The estimated annual public sector expenditure on asthma inhalers for adolescents and adults in 2024 was derived from the public sector tender contract estimates and associated public sector pricing data, and cross-verified with the National Department of Health.[14]

This analysis aims to compare the direct treatment costs of regular FP/salm plus as-needed SABA with those of MART from a payer's perspective, applying current SA public sector medicine prices and healthcare utilisation costs to data from published randomised controlled trials (RCTs) that have directly compared the two regimens.

# Methods

## Clinical trials

We conducted a targeted search of the Epistemonikos database on 21 April 2025 to identify RCTs comparing regular FP/salm plus as-needed SABA with MART in people with moderate/severe asthma aged ≥12 years. Search terms included 'fluticasone/salmeterol', 'maintenance and reliever therapy', 'MART', 'moderate asthma', 'severe asthma', 'randomised controlled trials' and 'RCTs' (the detailed search strategy is described in Appendix 1 of the supplementary material). We retrieved three records: one was excluded owing to an incorrect indication, another was a narrative review, and the third was a costing analysis (excluded studies with justification are listed in Appendix 2). A hand search of bibliographic citations of the excluded records identified three multicentre primary RCTs: AHEAD (NCT00242775),[15] COMPASS (AstraZeneca study SD-039-0735),[16] and COSMOS (AstraZeneca study SD-039-0691).[17] The study selection process is illustrated in the PRISMA flow diagram (Fig. 1). Table 1 summarises the characteristics of the three studies, which involve comparable patient populations. In all studies, the primary endpoint across studies was time to first severe exacerbation, defined as a deterioration in asthma resulting in hospitalisation/emergency room treatment, oral steroids for 3 days, or an unscheduled visit leading to treatment change. Additionally, all studies reported the rate of severe exacerbations per patient. Efficacy data from the three included RCTs are described in Table 1.

## Resource utilisation data

Resource utilisation data for the AHEAD, COMPASS and COSMOS RCTs were sourced from Wickstrøm *et al.*,[10] as granular data were not reported in the individual RCT publications. These data included healthcare visits, home visits, hospitalisation days, and ambulance transport. Resource use data were extrapolated to 12 months. Scheduled visits and tests outlined in the study protocols were excluded, as these were similar across the three studies. This analysis focuses on the SA public sector, considering only medicines listed in the public sector tender and applying local cost estimates for healthcare hospitalisation costs (Table 2). Table 2 reports the mean annual healthcare resource use per patient (expressed as events per patient per year) and the mean daily inhalation use per patient for study medications, as derived from the respective clinical trials. The terbutaline 0.4 mg metered dose inhaler is not listed on the public sector tender, and the therapeutic equivalent salbutamol 200 µg metered dose inhaler was therefore considered.[18]

## Economic analysis

A comparative cost analysis was conducted from a payer's perspective, specifically the public health sector in SA, focusing on direct costs related to medication and healthcare utilisation. The objective was to estimate the annual cost per patient of regular FP/salm plus as-needed SABA compared with bud/form used as MART for the SA setting. The time horizon for the economic analysis was 1 year, with the effectiveness measure defined as the number of severe exacerbations avoided per patient per year. Medication costs were sourced from the SA public sector tenders, converted to 2025 USD, while healthcare utilisation costs were sourced from the 2025 National Department of Health Uniform Patient Fee Schedule.[19] The unit costs for 2025 are described in Appendix 3. For each of the three studies, the cost of using bud/form MART was calculated as a percentage of using FP/salm plus as-needed SABA.

Additional information on the calculation of medication costs is provided in Appendix 6.

## Sensitivity analysis

To check whether our conclusions remain valid if cost assumptions change, we performed sensitivity analyses. We used both univariate (changing one variable at a time) and bivariate (changing two variables at a time) analyses. In the univariate analysis, we increased and decreased key cost parameters by 10% to see how sensitive the results were to changes in the price of bud/form MART, the cost per day of intensive care unit (ICU) and general ward hospitalisations, emergency room visits, and specialist consultations. Owing to limited

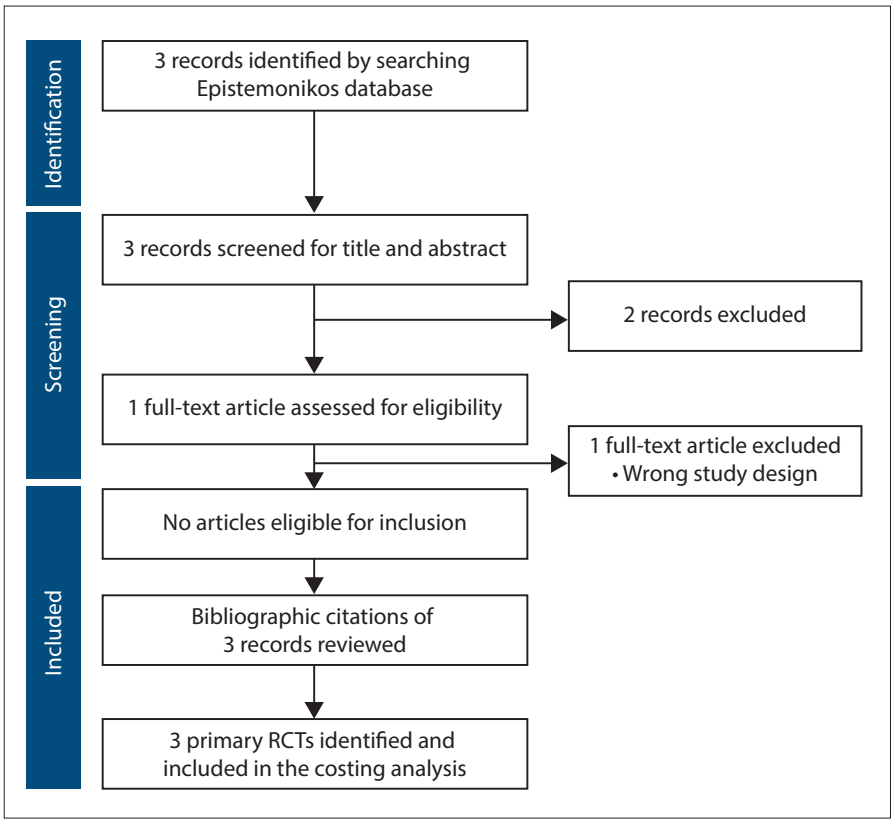


*Fig. 1. Selection of studies. (RCT = randomised controlled trial.)*

local data for public sector hospitalisation costs, we performed additional bivariate sensitivity analyses, simultaneously changing the ICU and ward costs. For this analysis, we used higher hospitalisation costs estimated by Cleary *et al.*,[20] inflated to 2024 values. Cleary *et al.*[20] based their estimates on the Health Systems Trust District Health Barometer (HST-DHB) (12th edition, 2016/17), which reports hospital-level expenditure per patient-day equivalent across different levels of public hospitals.[21] These costs were adjusted to 2020 prices using the Consumer Price Index. A weighted average unit cost was calculated, based on the proportion of usable beds at each level of care. As the HST-DHB data do not include ICU-specific costs, Cleary *et al.*[20] estimated the unit cost per ICU day by taking the difference between ICU and general ward tariffs in the private sector and applying it to public sector hospital costs.

## Results

Based on current public sector prices, the annual total direct treatment costs per patient for bud/form MART were comparable to those for maintenance FP/salm plus as-needed SABA in both the COMPASS[16] and COSMOS[17] studies. The average cost was USD145.84 v. USD157.81 per patient, respectively. In COMPASS, low to moderate doses were used – bud/form 160/4.5 µg 12-hourly as maintenance, with additional inhalations as needed, compared with FP/salm 250/50 µg 12-hourly, plus as-needed SABA. COSMOS allowed physicians to titrate maintenance doses of both regimens based on clinical judgement. In contrast, the AHEAD[15] study used higher maintenance doses, resulting in higher annual costs. Two inhalations of bud/form 160/4.5 µg 12-hourly translated into direct annual treatment costs of USD149.14, compared with USD122.65 for the twice-daily regimen of FP/salm 500/50 µg. Medication costs were the main cost drivers, with MART being more expensive than FP/salm plus as-needed SABA (Table 3). Fig. 2 compares the total direct treatment costs for each treatment arm in the three studies.

We tested the robustness of the analysis using several univariate sensitivity analyses. The findings of the univariate sensitivity analyses are presented in Appendix 4. Overall, the results were consistent. and did not change the main conclusions. However, the price of bud/form 160/4.5 µg emerged as a major cost driver, with the total cost of bud/form MART being highly sensitive to changes in its price. The results of the bivariate sensitivity analysis are presented in Appendix 5. Using the higher hospitalisation cost estimates from Cleary *et al.*[20] (ICU: ZAR22 448 v. ZAR19 319 in the base case; general ward: ZAR4 689 v. ZAR3 102) increased the absolute costs of treatment across all groups. However, the cost difference between the FP/salm and bud/form MART treatment groups remained minimal across all three trials. This finding suggests that, although overall treatment cost estimates depend on the unit cost assumptions, the two treatment strategies remain cost-neutral regardless of the cost data source. This means that switching to bud/form MART does not significantly change overall healthcare costs under either cost assumption scenario.

## Discussion

This comparative cost analysis, informed by clinical trial data and unit cost estimates from the SA public sector, showed that the total direct costs of bud/form 160/4.5 µg MART were comparable to regular FP/salm plus as-needed SABA for adults with moderate to severe asthma. In contrast, the higher maintenance regimen of bud/form (320/9 µg 12-hourly), with as-needed bud/form 160/4.5 µg, was more costly than FP/salm (500/50 µg) plus as-needed SABA in the AHEAD study.[15] The increased costs in the high-dose MART arm were primarily driven by medication acquisition costs, despite the lower rates of severe asthma exacerbation.

Although asthma-associated hospitalisations incur significant costs, healthcare resource use in the evaluated cohorts was low overall. This finding aligns with the relatively low rates of severe exacerbations reported across studies. Our analysis indicated that medication costs were the most important driver contributing to direct costs. Across the three included studies, the mean cost saving associated with FP/salm plus as-needed SABA was 0.58% relative to bud/form MART, suggesting that the procurement price of bud/form (160/4.5 µg) in the SA public sector is generally cost-aligned. However, sensitivity analysis indicated that a 10% reduction in the acquisition cost of bud/form 160/4.5 µg significantly influenced cost-efficiency, suggesting price sensitivity

**Table 1. Characteristics of included studies**

| | Study | | |
|---|---|---|---|
| | **AHEAD**[15] | **COMPASS**[16] | **COSMOS**[17] |
| Author, year | Bousquet *et al.*, 2007 | Kuna *et al.*, 2007 | Vogelmeier *et al.*, 2005 |
| Countries/sites (*n*) | 17/184 (*n*=2 309) | 16/235 (*n*=3 335) | 16/246 (*n*=2 143) |
| Study design | Randomised, double blind, parallel group | Randomised, double blind, double dummy, parallel group | Randomised, open label, parallel group |
| Patient population | | | |
| Age (years), mean (range) | 39 (12 - 80) | 38 (11 - 83) | 45 (12 - 84) |
| Mean baseline FEV1, predicted (%) | 71 | 73 | 73 |
| Patient inclusion criteria | Persistent asthma treated with ICS alone (800 - 1 600 µg/d) or ICS (400 - 1 000 mg/d) plus LABA for ≥3 months before study entry<br>A pre-bronchodilator FEV1 ≥50% of predicted normal value, with ≥12% reversibility following 1 mg terbutaline, and ≥1 clinically important asthma exacerbation (as judged by the clinician) in the previous 12 months (but none in the month before enrolment)<br>At the end of the run-in, patients had to have used as-needed terbutaline on ≥5 of the previous 7 days, with ≤8 inhalations in any single day | Asthma diagnosis (as defined by the ATS) for ≥6 months and using ICS for ≥3 months (≥500 µg/d of budesonide/fluticasone, or ≥1 000 µg/d of another ICS) for ≥1 month<br>An FEV1 ≥50% of predicted normal with ≥12% reversibility following terbutaline 1 mg and ≥1 asthma exacerbation in the previous 1 - 12 months<br>Patients using reliever(s) on ≥5 of the last 7 days of the 2-week run-in | Diagnosis of asthma (as defined by the ATS) for ≥6 months and using ≥500 µg/day of budesonide/fluticasone (or ≥1 000 µg of another ICS) for ≥1 month before study entry<br>A pre-terbutaline FEV1 40 - 90% of predicted normal value<br>At least one severe exacerbation >2 weeks but ≤12 months before study entry<br>As-needed medication on ≥4 of the last 7 days of run-in |
| Intervention arm* | Bud/form 160/4.5 µg, 2 inhalations 12-hourly + 1 inhalation as needed (MART) | Bud/form 160/4.5 µg, 1 inhalation 12- hourly + 1 inhalation as needed (MART) | Bud/form 160/4.5 µg, 1 - 2 inhalations 12-hourly + 1 inhalation as needed (MART) |
| Comparison arm* | FP/salm 500/50 µg 12-hourly + terbutaline 0.4 mg as needed | FP/salm 125/25 µg, 2 inhalations 12-hourly + terbutaline 0.4 mg as needed | FP/salm 250/50 µg or 100/50 µg or 100/50 µg or 500/50 µg 12-hourly + salbutamol 200 µg as needed |
| Follow-up duration | 6 months† | 6 months† | 12 months |
| Primary endpoint | Time to first severe exacerbation‡ | | |
| Results, FP/salm v. MART | Patients with severe exacerbation(s) 130/1 153 (11.3%) v. 108/1 151 (9.4%)<br>Rate, events/100 patients/year 31 v. 25 | Patients with severe exacerbation(s) 138/1 123 (12.3%) v. 94/1 105 (8.5%)<br>Rate, events/100 patients/year 38 v. 24 | Patients with severe exacerbation(s) 204/1 076 (19.0%) v. 159/1 067 (14.9%)<br>Rate, events/100 patients/year 23 v. 19 |
| Funding | AstraZeneca | | |

*n* = number of study participants; FEV1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; LABA = long-acting beta-2-agonist; ATS = American Thoracic Society; bud/form = budesonide + formoterol; MART = maintenance and reliever therapy; FP/salm = fluticasone + salmeterol.

*Only data from the relevant intervention and comparison treatment arms are included.

†Data extrapolated to 12 months.

‡Time to first severe exacerbation was longer with MART compared with FP/salm in the COSMOS and COMPASS studies, but there was little to no difference between groups in the AHEAD study.

with an opportunity to negotiate prices in the current procurement framework.

Economic evaluations conducted in high-income countries have reported MART as the dominant strategy compared with FP/salm, attributed to comparable medication costs and reduced exacerbation-related healthcare utilisation.[6-9,22-24] However, country-specific analyses from Thailand, Vietnam and Indonesia have reported lower acquisition costs for FP/salm relative to bud/form, thereby favouring the FP/salm regimen in these settings.[11,12] Furthermore, an SA retrospective study at Groote Schuur Hospital of severe asthmatics requiring ICU ventilation found that most patients were young adults. Preventable risks were identified as underuse of ICS (only 60%), smoking (36.4%), substance abuse (14.5%), poor outpatient care and follow-up (61.5%), and insufficient or delayed early care.[25]

To support evidence-informed policy and procurement decisions, future research should prioritise budget impact analyses incorporating country-specific epidemiological data, healthcare utilisation patterns, and cost assessments. This would provide critical insights into the

**Table 2. Average resource use per patient by treatment option in each study***

| | Study | | | | | |
|---|---|---|---|---|---|---|
| | AHEAD[15] | | COMPASS[16] | | COSMOS[17] | |
| Resource | FP/salm + terbutaline | Bud/form MART | FP/salm + terbutaline | Bud/form MART | FP/salm + salbutamol | Bud/form MART |
| Annual healthcare use per patient | | | | | | |
| Ambulance | - | - | 0.022 | 0.006 | - | - |
| Hospitalisation | | | | | | |
| Intensive care | 0 | 0.010 | 0.012 | 0.048 | 0.005 | 0.009 |
| General ward | 0.050 | 0.060 | 0.296 | 0.074 | 0.09 | 0.05 |
| Healthcare | | | | | | |
| Emergency room | 0.104 | 0.094 | 0.178 | 0.134 | 0.06 | 0.04 |
| Specialist | 0.240 | 0.152 | 0.408 | 0.314 | 0.24 | 0.17 |
| General care physician | 0.192 | 0.168 | 0.096 | 0.074 | 0.10 | 0.05 |
| Other healthcare personnel | 0.056 | 0.028 | 0.096 | 0.074 | 0.01 | 0 |
| Home visits | | | | | | |
| General care physician | 0.016 | 0.010 | 0.016 | 0.026 | 0.04 | 0.03 |
| Other healthcare personnel | 0.006 | 0.002 | 0.044 | 0.006 | 0.01 | 0 |
| Daily medication use per patient | | | | | | |
| Bud/form MART 160/4.5 µg | - | 4.879 | - | 3.250 | - | 3.940 |
| FP/salm 125/25 µg | - | - | 4.304 | - | - | - |
| FP/salm 100/50 µg | - | - | - | - | 0.233 | - |
| FP/salm 250/50 µg | - | - | - | - | 1.214 | - |
| FP/salm 500/50 µg | 1.978 | - | - | - | 0.490 | - |
| Salbutamol 200 µg | - | - | - | - | 0.907 | - |
| Terbutaline 0.4 mg | 0.995 | - | 1.036 | - | - | - |

FP/salm = fluticasone + salmeterol; bud/form MART = budesonide + formoterol maintenance and reliever therapy.
*Values in Table 2 represent the mean annual number of events per patient (e.g. hospitalisations, emergency room visits) or the mean number of inhalations per patient per day for maintenance and reliever medications. For example, a value of 0.022 indicates an average of 0.022 events per patient per year (~2.2 events per 100 patients annually).

**Table 3. Average annual total direct costs per treatment option in each study**

| Treatment arm | Medication costs (USD) | Healthcare costs (USD) | Total direct treatment costs (USD) | Savings of FP/salm v. bud/form MART, % |
|---|---|---|---|---|
| AHEAD[15] | | | | |
| FP/salm + as-needed SABA | 76.88 | 45.77 | 122.65 | 17.8 |
| Bud/form MART | 96.40 | 52.73 | 149.14 | |
| COMPASS[16] | | | | |
| FP/salm + as-needed SABA | 62.34 | 125.75 | 190.09 | –7.8 |
| Bud/form MART | 64.21 | 112.16 | 176.37 | |
| COSMOS[17] | | | | |
| FP/salm + as-needed SABA | 77.27 | 48.26 | 125.53 | –8.9 |
| Bud/form MART | 77.85 | 37.47 | 115.31 | |

FP/salm = fluticasone + salmeterol; SABA = short-acting beta-2-agonist; bud/form MART = budesonide + formoterol maintenance and reliever therapy.

affordability and cost-efficiency of asthma treatment strategies, while considering local resource constraints and health system priorities.

This analysis has several limitations. It was conducted solely from the perspective of the SA public health sector and does not reflect cost dynamics in the private sector. Since medicine pricing and healthcare service tariffs differ substantially between sectors, our findings may not be generalisable to the broader healthcare system or patients accessing care privately. The analysis focused exclusively on direct healthcare costs, including medication and healthcare utilisation, and excluded indirect costs such as productivity losses from missed work or school days, caregiver time or long-term disability, which are relevant when considering a societal perspective. Furthermore, it included only adolescent and adult patients with moderate to severe asthma. As a result, the full economic burden of asthma and the potential cost savings from preventing asthma exacerbations may be underestimated. Clinical trial data, used for resource utilisation and treatment effects, may not reflect real-world adherence, prescribing behaviours or health system constraints, impacting on both cost and effectiveness outcomes. The assumption of complete adherence to prescribed therapies could further bias cost estimates. Additionally,

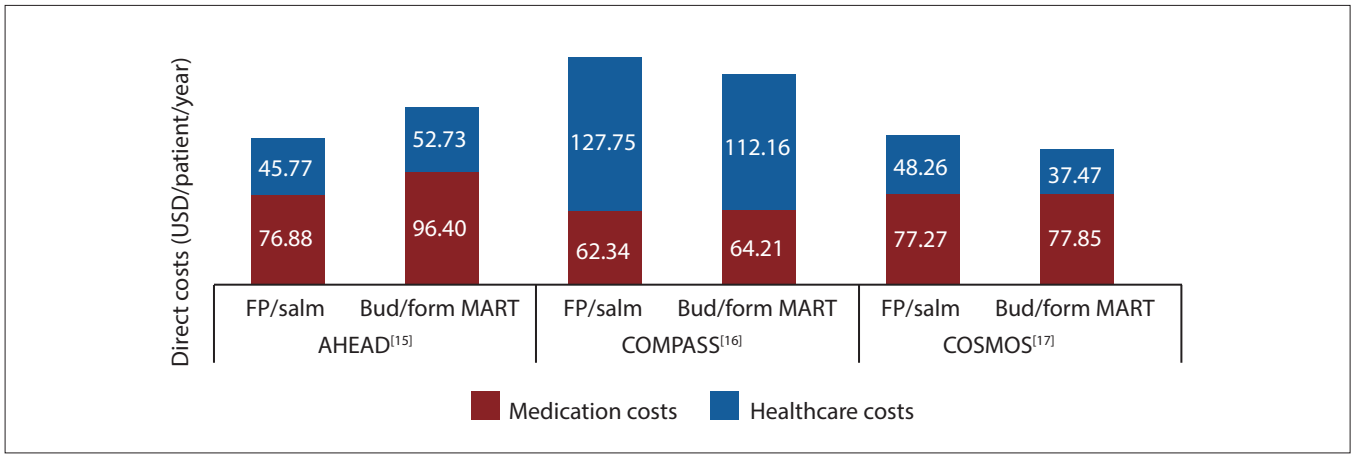


*Fig. 2. Average total direct costs per treatment option in each study. (FP/salm = fluticasone + salmeterol; bud/form MART = budesonide + formoterol maintenance and reliever therapy.)*

while univariate sensitivity analyses were performed, probabilistic sensitivity analyses were not conducted, limiting the assessment of uncertainty. Future research incorporating broader uncertainty analyses and real-world data would help validate these findings and enhance their applicability to policy decision-making.

## Conclusion

This comparative cost analysis, using public sector pricing and clinical trial data, found that the annual direct treatment costs of bud/form MART were comparable to, and in some cases higher than, those of FP/salm plus as-needed SABA for moderate to severe asthma, using costing data from SA. The primary cost driver was medication costs, with bud/form MART being particularly sensitive to price fluctuations. These findings emphasise the importance of procurement pricing in determining cost efficiency and support ongoing negotiations to improve affordability. Future research should incorporate real-world data with a broader range of cost components, alongside cost-effectiveness and budget impact analyses for various asthma treatment strategies. Such evaluations should be informed by contextual epidemiological data and reflect the full continuum of the stepwise asthma approach. This would guide sustainable, evidence-based asthma treatment policies within the evolving context of universal health coverage.

**Data availability.** All data used in this study were obtained from publicly available sources listed in the manuscript, and any generated data are included in the published article or its supplementary information.

**Declaration.** None.

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**Author contributions.** Conceptualisation: TDL (PhD candidate), DB; data curation: TDL; analysis and interpretation of the data: TDL, DB; drafting the initial article: TDL; revising the article for important intellectual context: DB; final approval of the version of the article to be published: TDL, DB.

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**Conflicts of interest.** None.

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