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Original Article

Long-Term Cost-Effectiveness of Digital Inhaler Adherence Technologies in Difficult-to-Treat Asthma

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What is already known about this topic? Electronic monitoring devices such as digital inhalers can monitor and support medication adherence and inform step-up treatment decisions (eg, to add-on biologics) in difficult-to-treat asthma. Whereas short-term benefits have been shown, long-term cost-effectiveness of digital inhalers is unknown.

What does this study adds to our knowledge? This is the first study demonstrating the cost-effectiveness of digital inhaler adherence-enhancing strategies in patients with difficult-to-treat asthma. Scenario analyses all resulted in cost-savings even when assumptions on long-term effects regarding asthma control, exacerbations, and introduction of biosimilars were varied.

How this study impact current management guidelines? Based on our results, reimbursement of digital inhalers could be considered for difficult-to-treat asthma patients. Furthermore, the model we developed enables clinicians, policy makers, and researchers to evaluate the cost-effectiveness of other digital adherence-enhancing strategies in asthma management.

BACKGROUND: Digital inhalers can monitor inhaler usage, support difficult-to-treat asthma management, and inform step-up treatment decisions yet their economic value is unknown, hampering wide-scale implementation.

OBJECTIVE: We aimed to assess the long-term cost-effectiveness of digital inhaler–based medication adherence management in difficult-to-treat asthma.

METHODS: A model-based cost-utility analysis was performed. The Markov model structure was determined by biological and clinical understanding of asthma and was further informed by guideline-based assessment of model development. Internal and external validation was performed using the Assessment of the Validation Status of Health-Economic (AdViSHE) tool. The INCA (Inhaler Compliance Assessment) Sun randomized clinical

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Conflicts of interest: R. W. Costello has a patent Acoustic method to assess adherence issued; a patent Method to quantify adherence issued; and a patent Method to predict exacerbations issued. J. W. H. Kocks reports grants, personal fees, and nonfinancial support from AstraZeneca, Boehringer Ingelheim, and GlaxoSmithKline (GSK); grants and personal fees from Chiesi Pharmaceuticals, and TEVA; personal fees and nonfinancial support from Mundi Pharma; personal fees from Merck, Sharp, and Dohme (MSD) and COVIS Pharma; grants from Valneva, outside the submitted work; and holds less than 5% shares of Lothar Medtec GmbH and 72.5% of shares in the General Practitioners Research Institute. M. J. Postma holds 25% shares of HealthEcore and 100% of shares of PAG B.V. J. F. M. van Boven reports grants from Aardex; grants from European Commission COST Action CA19132 "ENABLE", grants and personal fees from AstraZeneca, Chiesi, and Novartis; and personal fees from GSK, Teva, Trudell Medical and Vertex, outside the submitted work. The rest of the authors declare that they have no relevant conflicts of interest.

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Abbreviations used
ACT- Asthma Control Test
AdViSHE- Assessment of the Validation Status of Health-Economic decision models
ED- Emergency department
ICER- Incremental cost-effectiveness ratio
ICS- Inhaled corticosteroids
INCA- Inhaler Compliance Assessment
LABA- Long-acting beta-agonist
QALY- Quality-adjusted life years

trial data were incorporated into the model to evaluate the cost-effectiveness of digital inhalers. Several long-term clinical case scenarios were assessed (reduced number of exacerbations, increased asthma control, introduction of biosimilars [25% price-cut on biologics]).
RESULTS: The long-term modelled cost-effectiveness based on a societal perspective indicated 1-year per-patient costs for digital inhalers and usual care (ie, regular inhalers) of €7,546 ($7,946) and €10,752 ($11,322), respectively, reflecting cost savings of €3,207 ($3,377) for digital inhalers. Using a 10-year intervention duration and time horizon resulted in cost savings of €26,309 ($27,703) for digital inhalers. In the first year, add-on biologic therapies accounted for 69% of the total costs in the usual care group and for 49% in the digital inhaler group. Scenario analyses indicated consistent cost savings ranging from €2,287 ($2,408) (introduction biosimilars) to €4,581 ($4,824) (increased control, decreased exacerbations).
CONCLUSIONS: In patients with difficult-to-treat asthma, digital inhaler–based interventions can be cost-saving in the long-term by optimizing medication adherence and inhaler technique and reducing add-on biologic prescriptions. **(J Allergy Clin Immunol Pract 2023;11:3064-73)**

Key words: *Asthma; Cost-effectiveness,; Adherence; Smart inhaler; Digital; Electronic monitoring; eHealth*

INTRODUCTION

Asthma is the most prevalent chronic respiratory disease worldwide, affecting more than 300 million adults and children.[1] Despite the availability of effective inhaled treatment, nearly half of the patients with asthma remain inadequately controlled.[2] Suboptimal disease control is associated with significant costs and is often the result of poor medication adherence.[3] Medication adherence is important to maximize the benefits of asthma therapy and should be optimized before initiating more costly (biologics) or harmful (oral corticosteroids, high-dose inhaled corticosteroids [ICS]) therapy.[4,5] Therefore, clinical guidelines recommend regular assessment of medication adherence.[6] Nevertheless, real-world adherence rates remain low.[7] Nonadherence is a complex and multifactorial problem and requires careful monitoring and management strategies, such as reminders, education, action plans, and inhaler technique training.[8] Given the heterogeneity in patients' needs, preferences, and capabilities, a personalized approach is necessary.[8]

Novel digital e-health technologies are likely to facilitate this personalized approach.[9] Recent developments are electronic monitoring devices or digital "smart" inhalers that provide real-time feedback on medication usage and can help distinguish difficult-to-treat asthma (ie, uncontrolled asthma despite medium- or high-dose ICS in combination with a second controller such as a long-acting beta-agonist [LABA], which is often the result of modifiable factors such as poor medication adherence, incorrect inhaler technique, or untreated comorbidities) from severe asthma (ie, uncontrolled asthma despite maximal optimized high-dose ICS/LABA treatment and management of modifiable factors).[10] Digital inhalers have shown to increase medication adherence,[10-15] and may potentially benefit clinical outcomes and reduce the economic burden in patients with difficult-to-treat asthma.[7] Indeed, in the recent 32-week INCA (Inhaler Compliance Assessment) Sun trial,[16] a digital inhaler strategy was found to improve medication adherence and reduce high-dose ICS and add-on biologic prescriptions. Although critical for wider-scale implementation in daily practice, long-term economic evidence on the value of digital inhalers is, however, still absent.

The aim of this study was to assess the long-term cost-effectiveness of digital inhaler–based management of patients with difficult-to-treat asthma.

METHODS

Study design

This was a long-term cost-effectiveness study using a Markov model. Model development adhered to The Professional Society for Health Economics and Outcomes Research (ISPOR) Modeling Good Research Practices on model conceptualization,[17] and the development of state-transition models.[18] This study was reported according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) reporting checklist (Table E1; available in this article's Online Repository at www.jaci-inpractice.org).

Study population

The population consisted of a hypothetical group of adults (age ≥ 18 y) with difficult-to-treat, uncontrolled asthma, being in Global Initiative for Asthma (GINA) step 4 (ie, using medium- or high-dose ICS/LABA treatment), receiving either the personalized adherence-enhancing intervention (ie, INCA Sun) or usual care. The model population consisted of 64% females and had a starting age of 47 years, in line with the population of the INCA Sun study.[16]

Setting and location

The INCA Sun study was a 32-week randomized controlled trial (n = 213) conducted between October 2015 and September 2020 in 10 severe asthma clinics across Ireland, Northern Ireland, and England. All participants received the digital INCA device (a digital adherence monitor), attached to their inhaler throughout the study.[16]

Comparators

The intervention group received personalized biofeedback based on digital inhaler–assessed medication adherence, inhalation technique, and peak expiratory flow. The control group received usual care (ie, adherence coaching, inhaler training, and action plan). In

the intervention group, treatment decisions were informed by digital data (ie, medication adherence, technique, and peak expiratory flow data) in combination with exacerbation history and self-reported asthma control. In the control group, decisions were made based on pharmacy refill rates in combination with exacerbation history and self-reported asthma control.

Summary of INCA Sun results

In short, the INCA Sun trial[16] showed that 11% of the intervention patients and 21% of the control patients required add-on biologic therapy at week 32 (odds ratio [OR] 0.42, 95% CI 0.189−0.95; $P = .038$). Patients were eligible for add-on biologic therapy at study end if, during the last 24 weeks of the study, (1) patients used at least 1 course of systemic corticosteroids for an exacerbation, (2) elevated biomarkers indicative of type 2 inflammation were found, (3) patients were uncontrolled (ie, Asthma Control Test [ACT] $\leq$ 19 in the control groups and mean electronically measured peak expiratory flow $<$ 80% personal best and ACT $\leq$ 19 in the intervention group), and (4) patients in the intervention group were adherent to high-dose ICS in combination with LABAs (ie, actual medication adherence rate $>$ 80%). The mean medication adherence rate between week 20 and week 32 was 64.9% in the intervention group and 55.5% in the control group (difference 9.4%, 95% CI 2.31−16.4; $P = .010$). No significant differences in asthma control or exacerbations were found between the 2 groups.[16]

Perspective and cycle length

In the base-case scenario, a Dutch societal perspective was applied, and also a health care payer's perspective was assessed.[19] Transition cycle lengths were 2 weeks, in line with previous models.[20,21] This cycle length ensures that the model resembles a real-world scenario as much as possible because typical exacerbation events mostly last less than 2 weeks (ie, low utility values and high costs associated to exacerbation states only apply for 2 wk).

Time horizon and duration of intervention

The time horizon was varied from 1 year to lifetime (ie, 60 y). Furthermore, duration of use of digital inhalers was varied from 1 year to lifetime. Adherence to the intervention program was assumed to stay constant across the intervention group throughout the use of the intervention. The effect of the intervention was assumed to end when the use of the intervention ended (ie, the level of medication adherence dropped to the usual care level and transition probabilities were adjusted accordingly).

Outcomes

The model calculated total discounted costs, number of exacerbations, and quality-adjusted life years (QALY) for usual care group and intervention. The incremental cost-effectiveness ratio (ICER) (ie, cost/QALY) was calculated to assess the cost-effectiveness of intervention compared with usual care.

Discount rate

Costs and QALY were discounted after 1 year follow-up at rates of 4.0% and 1.5%, respectively.[19]

Costs and currency

Costs included cost of the adherence-enhancing strategy (eg, the digital inhaler intervention), exacerbation events (ie, community-, emergency department [ED]−, or hospital-treated), asthma medication costs (including inhalers and biologics), general health care utilization costs (eg, general practitioner and pulmonologist visits). During follow-up, the proportion of patients that used biologics in the intervention and control groups was assumed to remain stable. In addition, the proportion of patients using biologic therapy in the intervention group increased to the level of usual care after the intervention stopped. The costs as provided in the INCA Sun study[16] were used where possible. In line with the INCA Sun trial cost calculations, open resource prices (mean wholesale acquisition cost) for the 5 biologics (benralizumab, dupilumab, mepolizumab, omalizumab, and reslizumab) that are currently available were used and converted to euros.[16] Average reference prices were used for costs that were not available in the INCA Sun data.[22] We also included indirect costs (ie, work absence because of asthma and patients with asthma being incapacitated).[19] To determine the costs due to patients being incapacitated, the friction cost method was applied. We made the following assumptions regarding indirect costs, owing to limited data availability: (1) controlled patients are not absent from work because of asthma, (2) controlled patients are not incapacitated to work because of asthma, and (3) the number of days patients are absent from work during exacerbations are 2 for a community-treated exacerbation, 3 for an ED-treated exacerbation, and 2 weeks for a hospital-treated exacerbation. A conservative estimate was made for work absence during nonexacerbation state for patients with uncontrolled disease based on data.[23,24] Indirect costs are applied to patients for the entirety of a patient's working life. All costs were adjusted to 2022 euros.

Rationale and description of the model

Based on a review of previous asthma cost-effectiveness models,[25] a new model was designed. The conceptualization of the model structure was determined by biological and clinical understanding of asthma and was further informed by guideline-based assessment of model development through expert consultation (ie, as suggested by the AdViSHE).[26] The Markov model was created with the statistical programming environment R version 3.5.1, and Microsoft Excel. It incorporates several aspects of previous models,[27] while also incorporating the clinical and economic impact of increased adherence of digital inhalers; suboptimal adherence rates directly impact medication costs, and indirectly impact clinical effects in the model (Figure 1).

Similar to the model developed by Zafari et al,[28] the model incorporates level of asthma control, exacerbations, and death as health states and calculates total costs as well as QALY. The model assumes 2 potential levels of asthma control (ie, controlled or uncontrolled). The exacerbation state comprises exacerbation states represented in the asthma policy model, each with distinct utilities, probabilities, and costs: (1) exacerbations that are community treated (ie, systemic corticosteroids), (2) exacerbations that lead to an ED visit, and (3) exacerbations that lead to hospitalization.[29] Health state utility values associated with each asthma health state (ie, controlled and uncontrolled disease and exacerbations) were derived from the ACCURATE study.[30]

The model assumes different transition probabilities for exacerbations in controlled versus uncontrolled patients. Transition probability matrices (asthma control states, exacerbations, and death) are presented in Table I. The probability for asthma-related mortality in controlled patients was assumed to be 0. The probability for other-cause death was based on national life tables and depended on age and sex distribution of the INCA Sun population.[16]

Validation of the model

The model was qualitatively validated as suggested by the AdViSHE tool (Table E2; available in this article's Online

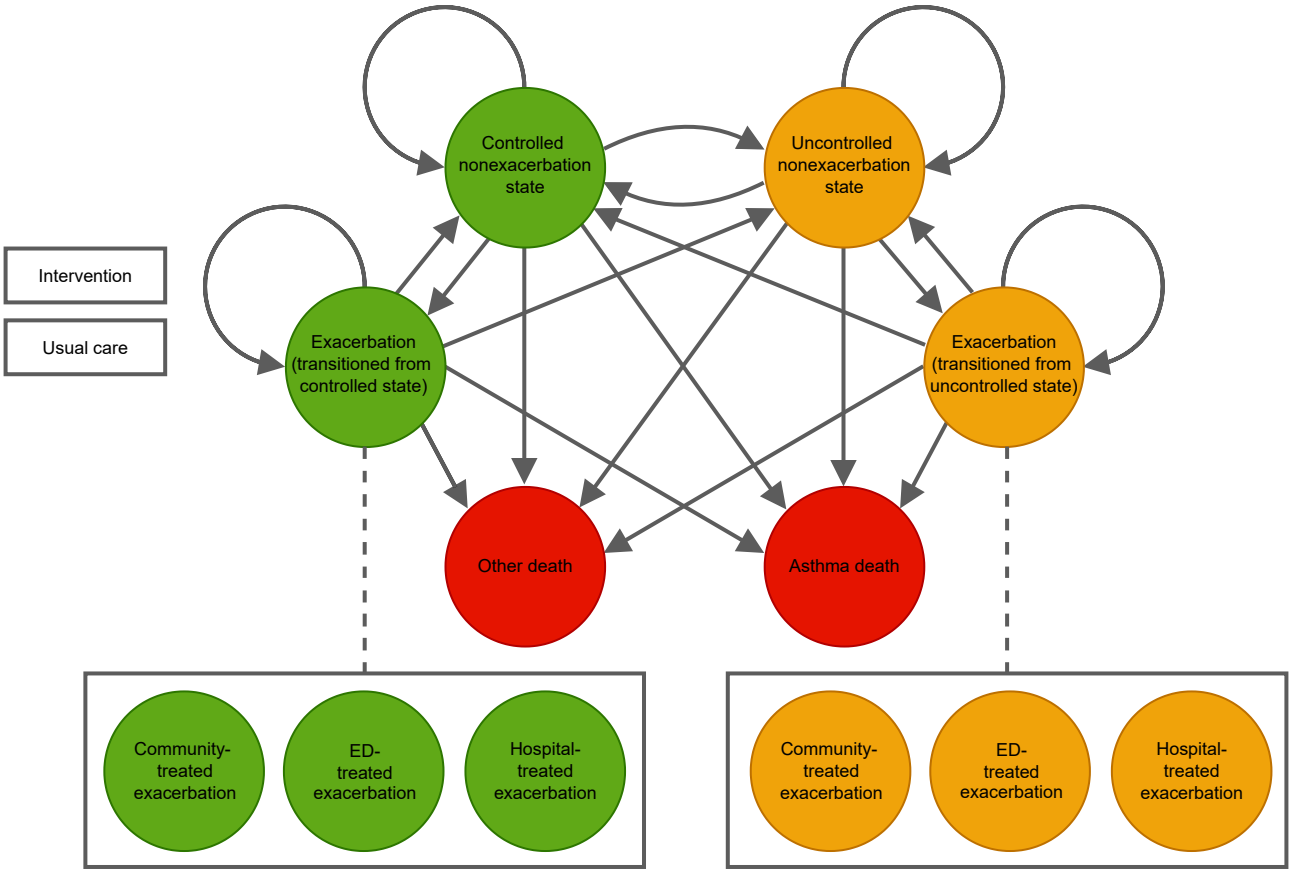

FIGURE 1. Schematic illustration of the model.

Repository at www.jaci-inpractice.org).[26] Face validity, input data, and outcomes were judged by clinical (ie, 2 pulmonologists and 1 general practitioner) and 2 health economic modeling experts. The internal validity of the simulation model was assessed by S. J. van de Hei, C. H. Kim, and J. F. M. van Boven through checking each of the calculations and functions in the model while also assessing the Markov traces regarding whether the appropriate numbers of patients were transitioning to each health state correctly. Extreme value and unit testing were performed (ie, setting transition probabilities to 0 and 1 and turning off specific costs and utilities as well as mortality). External validation was conducted by comparing model outcomes with empiric data using dependent (ie, data sources on which the model is based) and independent (ie, data sources which were not used to build the model) data. No other previous models incorporated the impact of digital inhalers on asthma control; therefore, cross-validation testing with other models was not possible.

Uncertainty, sensitivity, and scenario analyses

Univariate and probabilistic sensitivity analyses were performed to estimate the impact of parameter uncertainty on the results. In 1-way sensitivity analyses, 1 input parameter at a time was varied within its 95% CI to assess the influence of individual parameters. Outcomes were summarized in tornado diagrams, indicating the change in ICER per parameter, with parameters with the largest impact on top. In probabilistic sensitivity analyses, probability distributions were assigned to model parameters (Table I) and Monte Carlo simulation with 1,000 iterations was used to generate a random sample of model outcomes. Transition probabilities and utility parameters were assigned a beta distribution, which was generated from reported measures of sampling uncertainty (eg, standard errors and 95% CI). When such measures were not available, expert opinion was used to assign a plausible distribution. Cost parameters were assigned with gamma distributions. Various scenario analyses were performed in which the duration of digital inhaler use and the time horizon varied, and in which the effect of digital inhaler use on biologic prescriptions was varied (relative risk 0%−100%).

In addition to the main cost-effectiveness analysis of the INCA device intervention, we assessed 6 plausible clinical case scenarios and evaluated the long-term cost-effectiveness of these scenarios. These were (1) a 10% reduction in exacerbation rate in the intervention group after 1 year to simulate a possible long-term clinical effect of sustained enhanced adherence,[12,13,15] (2) a 5% reduction in exacerbation rate in the intervention group after 1 year, (3) an improvement in asthma control after 1 year to simulate possible long-term clinical effects of sustained enhanced adherence, with the improvement based on the asthma control improvement found in a previous digital inhaler study (ie, among initially uncontrolled adults 63% of the intervention patients were controlled after 1 year compared with 49% of the usual care group),[11] (4) half of the asthma control improvement as found in the study by Merchant et al[11] for the intervention group (ie, 56% of intervention patients are controlled after 1 year), (5) a combination of scenarios 1 and 3,

TABLE I. Population characteristics, utility values, costs,* and transition probabilities for the model

Parameter	Value	Probability distribution	Source
Population characteristics			
Age (y)	47	—	INCA Sun[16]
Proportion female (%)	64	—	INCA Sun[16]
Annual exacerbation rate for standard care	1.97	—	INCA Sun[16]
Proportion of patients using biologics			
Intervention	0.108	Percentage (±10%)	INCA Sun[16]
Usual care	0.214	Percentage (±10%)	INCA Sun[16]
Adherence to medication			
Intervention	0.649	Beta (70.09, 37.91)	INCA Sun[16]
Usual care	0.555	Beta (58.28, 46.73)	INCA Sun[16]
Proportion of asthma patients being incapacitated			
Controlled	0	-	Assumption[16]
Uncontrolled	0.026	Beta (1,556.54, 60,124.80)	[24,31]
Health state utility values			
Nonexacerbation			
Controlled	0.931	Beta (2,425.12, 180.88)	[30]
Uncontrolled	0.779	Beta (2,028.99, 577.01)	[30]
Exacerbation community treated	0.746	Beta (20.14, 6.86)	[30]
Exacerbation ED treated	0.658	Beta (7.77, 4.23)	[30]
Exacerbation hospital treated	0.571	Beta (1.71, 1.29)	[30]
Direct costs in € ($)/2-wk cycle			
General health utilization (nonexacerbation states)			
Controlled	10.47 (11.02)	Gamma (16, 0.65)	[22,31,32]
Uncontrolled	19.86 (20.91)	Gamma (16, 1.24)	[22,31,32]
Medication (nonexacerbation states)			
Intervention	39.80 (41.91)	Gamma (16, 2.49)	INCA Sun[16]
Controlled	40.98 (43.15)	Gamma (16, 2.56)	INCA Sun[16]
Biologics	1,331.00 (1,401.54)	Gamma (16, 83.19)	INCA Sun[16]
Exacerbation community-treated	148.33 (156.19)	Gamma (16, 9.27)	INCA Sun[16]
Exacerbation ED-treated	599.24 (631.00)	Gamma (16, 37.45)	[22], expert opinion
Exacerbation hospital-treated	4,419.14 (4,653.35)	Gamma (16, 276.20)	INCA Sun[16]
Intervention	15.34 (16.15)	Gamma (16, 0.96)	INCA Sun[16]
Indirect costs in € ($)/2-wk cycle			
Productivity loss (nonexacerbation state)			
Controlled	0	—	Assumption
Uncontrolled	22.90 (24.11)	Gamma (16, 1.43)	[22-24]
Being incapacitated	738.79 (777.95)	Gamma (16, 46.17)	[22,24,31]
Exacerbation community-treated	487.03 (512.84)	Gamma (16, 30.44)	[22], expert opinion
Exacerbation ED-treated	730.54 (769.26)	Gamma (16, 45.66)	[22], expert opinion
Exacerbation hospital-treated	2,435.15 (2,564.21)	Gamma (16, 152.20)	[22], expert opinion
Transition probabilities			
Uncontrolled to controlled			
Intervention	0.025	Beta (2.88, 110.12)	[11]
Standard care	0.025	Beta (2.88, 110.12)	[11]
Controlled to uncontrolled			
Intervention	0.006	Beta (0.50, 86.50)	[11]
Standard care	0.006	Beta (0.50, 86.50)	[11]
Asthma-related mortality			
Controlled	0	-	Expert opinion
Uncontrolled	2.29e-5	Beta (6.56, 286,283.44)	[24]
Exacerbation community-treated (uncontrolled state)	0.073	Beta (15.46, 196.54)	INCA Sun[16]
Exacerbation ED-treated (uncontrolled state)	5.05e-4	Beta (0.31, 609.69)	[30]

(continued)

TABLE I. *(Continued)*

Parameter	Value	Probability distribution	Source
Exacerbation hospital-treated (uncontrolled state)	0.003	Beta (0.68, 211.32)	INCA Sun[16]
RR of community-treated exacerbation (uncontrolled vs controlled)	1.51	Normal (1.35, 1.67)	[33]
RR of ED-treated exacerbation (uncontrolled vs controlled)	2.31	Normal (1.56, 3.06)	[33]
RR of hospital-treated exacerbation (uncontrolled vs controlled)	1.33	Normal (0.66, 2.00)	[33]

beta (x,y), Beta distribution with shape1(alpha) parameter x and shape2 (beta) parameter y; *gamma (x,y),* gamma distribution with shape parameter x and rate parameter y; *percentage (±10%),* an uncertainty of plus and minus 10% is accounted for; *normal (x,y),* normal distribution with 95% CI; *RR,* relative risk.
*All costs are adjusted to July 2022 euros.

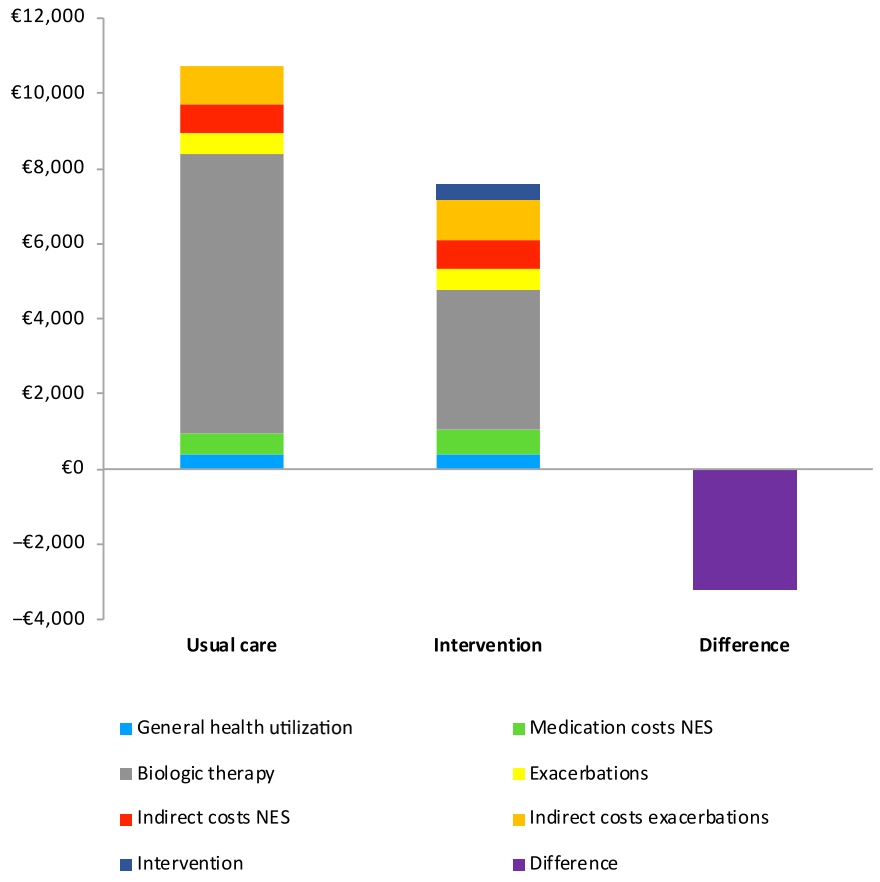

FIGURE 2. The 1-y total costs per patient for INCA Sun intervention and usual care from a societal perspective. *NES,* Nonexacerbation state. Usual care: general health utilization (€418 [$440]); medications costs NES (€549 [$578]); biologic therapy (€7,408 [$7,801]); exacerbations (€586 [$617]); indirect costs NES (€764 [$804]); indirect costs exacerbations (€1,027 [$1,081]); intervention (0), and total costs (€10,752 [$11,322]). Intervention: general health utilization (€418 [$440]); medications costs NES (€624 [$657]); biologic therapy (€3,728 [$3,926]); exacerbations (€586 [$617]); indirect costs NES (€764 [$804]); indirect costs exacerbations (€1,027 [$1,081]); intervention (€399 [$420]); and total costs (€7,546 [$7,946]). Difference total costs (−€3,207 [−$3,377])

and (6) a 25% reduction in price of biologic therapies to simulate the introduction of biosimilars.[34] For all scenarios, a societal perspective, an intervention duration of 1 year, and a 10-year time horizon were applied.

RESULTS

Study parameters

Table I shows the full list of parameters used to populate the cost-effectiveness model.

Summary of main results

From a societal perspective and for a 1-year intervention duration, total per-patient costs for intervention and usual care varied from €7,546 ($7,946, using the average € to US$ exchange rate [€1 = US$1.053] for 2022) to €10,752 ($11,322), respectively, for a 1-year time horizon. This reflects a cost saving of €3,207 ($3,377) per patient for the intervention (Figure 2). Biologics accounted for 69% of the total costs in the usual care group and for 49% in the intervention group in the first year. When modelling a 5-year intervention duration and a 5-year

TABLE II. Scenario analyses for the INCA Sun program (costs are discounted after 1 y)

Duration of intervention (y)*	Time horizon (y)*	RR of biologic use (digital inhaler vs usual care)	Costs (euros [U.S. dollars])		
			Intervention	Usual care	Difference
Societal perspective					
1	1	0.50	7,546 (7,946)	10,752 (11,322)	−3,207 (−3,377)
1	5	0.50	42,781 (45,048)	45,988 (48,425)	−3,207 (−3,377)
1	10	0.50	78,891 (83,072)	82,098 (86,449)	−3,207 (−3,377)
1	Lifetime	0.50	181,438 (191,054)	184,645 (194,431)	−3,207 (−3,377)
5	5	0.50	31,440 (33,106)	45,988 (48,425)	−14,548 (−15,319)
5	10	0.50	67,550 (71,130)	82,098 (86,449)	−14,548 (−15,319)
5	Lifetime	0.50	170,097 (179,112)	184,645 (194,431)	−14,548 (−15,319)
10	10	0.50	55,789 (58,746)	82,098 (86,449)	−26,309 (−27,703)
10	Lifetime	0.50	158,336 (166,728)	184,645 (194,431)	−26,309 (−27,703)
Lifetime	Lifetime	0.50	124,277 (130,864)	184,645 (194,431)	−60,368 (−63,568)
Different RR of biologic use					
1	10	0.00	75,163 (79,147)	82,098 (86,449)	−6,935 (−7,303)
1	10	0.25	77,015 (81,097)	82,098 (86,449)	−5,083 (−5,352)
1	10	0.75	80,719 (84,997)	82,098 (86,449)	−1,379 (−1,451)
1	10	1.00	82,571 (86,947)	82,098 (82,449)	473 (498)
Payer's perspective					
1	1	0.50	5,755 (6,060)	8,961 (9,436)	−3,207 (−3,377)
1	5	0.50	36,856 (38,809)	40,063 (42,186)	−3,207 (−3,377)
1	10	0.50	69,189 (72,856)	72,395 (76,232)	−3,207 (−3,377)
1	Lifetime	0.50	161,945 (170,528)	165,152 (173,905)	−3,207 (−3,377)
5	5	0.50	25,515 (26,867)	40,063 (42,186)	−14,548 (−15,319)
5	10	0.50	57,848 (60,914)	72,395 (76,232)	−14,548 (−15,319)
5	Lifetime	0.50	150,604 (158,586)	165,152 (173,905)	−14,548 (−15,319)
10	10	0.50	46,087 (48,530)	72,395 (76,232)	−26,309 (−27,703)
10	Lifetime	0.50	138,843 (146,202)	165,152 (173,905)	−26,309 (−27,703)
Lifetime	Lifetime	0.50	104,784 (110,338)	165,152 (173,905)	−60,368 (−63,568)

RR, Relative risk.
*A time horizon of 60 y was used for a lifetime horizon.

time horizon, a cost saving of €14,548 ($15,319) was found (Figure E1; available in this article's Online Repository at www.jaci-inpractice.org), and when modelling a 10-year intervention duration and a 10-year time horizon, a cost saving of €26,309 ($27,703) was found. No difference in QALY was found, because there was no difference between the intervention and the control groups in asthma control level and number of exacerbations. Table II shows the results of the scenario analyses, in which duration of intervention use and time horizon were varied for both the society's and the payer's perspective up to lifetime, and in which the effect of digital inhaler use on biologic prescriptions was varied. From a payer's perspective, total costs per patient for both groups were similarly lower because indirect costs were comparable for both groups (ie, owing to no difference in asthma control level and number of exacerbations between groups). All applied scenarios indicated cost savings, except for the scenario in which no effect of digital inhalers on biologic prescriptions was assumed.

Clinical case scenarios

The results of the 6 clinical case scenarios are presented in Table III. The intervention resulted in an increase in 0.007, 0.045, and 0.052 QALY for scenario 1 (10% reduction in exacerbation rate for the intervention group after 1 y), 3 (improvement in asthma control for the intervention group after 1 year), and 5 (combination of scenarios 1 and 3), respectively, with ICERs all indicating cost savings. Furthermore, use of the intervention resulted in 1.308, 0.215, and 1.502 fewer exacerbations per patient for scenario 1, 3, and 5, respectively. Cost savings were also found when the reduction in exacerbation rate was only 5% (scenario 2) and when the improvement of asthma was half of the improvement found in a previous study (scenario 4). No difference in QALY or exacerbations was found in scenario 6 (25% reduction in the price of biologic therapies) because this scenario only involved an adjustment in biologics cost. Table E3 (available in this article's Online Repository at www.jaci-inpractice.org) shows the results of the clinical case scenarios when modelling an intervention duration of 1 year and a 5-year time horizon.

Effects of uncertainty

One-way sensitivity analyses for clinical case scenario 1, 3, and 5 showed that the model was most sensitive to the 4 variables "probability of going from uncontrolled to controlled asthma for the usual care group," "probability of going from controlled to uncontrolled asthma for the usual care group," "cost of biologics," and "proportion of patients using biologics in the usual care group" (Figure E2; available in this article's Online

TABLE III. Scenario analyses based on clinical cases from a societal perspective with an intervention duration of 1 y and a 10-y time horizon

Outcome parameter	Usual care	Intervention	Difference
Scenario 1 (10% reduction in exacerbations in intervention group after 1 y)			
Total costs (euros [U.S. dollars])	82,098 (86,449)	77,987 (82,120)	−4,111 (−4,329)
QALY	8.082	8.088	0.007
Number of exacerbations	14.951	13.643	1.308
ICER		Cost-saving	
Scenario 2 (5% reduction in exacerbations in intervention group after 1 y)			
Total costs	82,098 (86,449)	78,440 (82,597)	−3,658 (−3,852)
QALY	8.082	8.085	0.003
Number of exacerbations	14.951	14.297	0.654
ICER		Cost-saving	
Scenario 3 (improved asthma control as found by Merchant et al[11] in intervention group after 1 y)			
Total costs	82,098 (86,449)	78,410 (82,566)	−3,688 (−3,883)
QALY	8.082	8.127	0.045
Number of exacerbations	14.951	14.735	0.215
ICER		Cost-saving	
Scenario 4 (50% of the improvement in asthma control as found by Merchant et al[11] in intervention group after 1 y)			
Total costs	82,098 (86,449)	78,765 (82,940)	−3,333 (−3,510)
QALY	8.082	8.093	0.012
Number of exacerbations	14.951	14.897	0.053
ICER		Cost-saving	
Scenario 5 (improved asthma control and 10% reduction in exacerbations in intervention group after 1 y)			
Total costs	82,098 (86,449)	77,517 (81,625)	−4,581 (−4,824)
QALY	8.082	8.134	0.052
Number of exacerbations	14.951	13.449	1.502
ICER		Cost-saving	
Scenario 6 (biosimilar introduction)			
Total costs	66,852 (70,395)	64,566 (67,988)	−2,287 (−2,408)
QALY	8.082	8.082	0.000
Number of exacerbations	14.951	14.951	0.000
ICER		Cost-saving	

Repository at www.jaci-inpractice.org). The results of the probabilistic sensitivity analyses for the clinical case scenarios are shown in cost-effectiveness planes in Figure E3 (available in this article's Online Repository at www.jaci-inpractice.org). Scatterplots show that, for a 10-year time horizon and 1-year intervention use, 54.4%, 57.4%, and 60.3% of the iterations in scenarios 1, 3, and 5, respectively, were positioned in the southeastern quadrant, indicating that the intervention is likely to be more effective and saving costs. Moreover, 0.2%, 0.0%, and 0.0% of the iterations for scenarios 1, 3, and 5, respectively, were positioned in the northeastern quadrant, indicating that the intervention is highly unlikely to result in higher costs in combination with greater effect. Figure E4 (available in this article's Online Repository at www.jaci-inpractice.org) shows the results of a scenario analyses for the clinical case scenarios, in which the duration of intervention use was varied from 1 to 60 months, and the time horizon was varied from 1 to 60 years (ie, lifetime). All indicated cost savings.

DISCUSSION

In this study, we assessed the long-term cost-effectiveness of digital inhaler–based adherence-enhancing interventions in patients with difficult-to-treat asthma and found cost savings between €3,207 ($3,377) (1-y time horizon, 1-y intervention duration) and €26,309 ($27,703) (10-y time horizon and intervention duration) per patient. Equal effectiveness was found between the intervention and the usual care groups, which is in line with the INCA Sun clinical trial[16] that demonstrated no short-term differences in clinical end points (ie, asthma control level and number of exacerbations). Although the intervention entailed certain costs, these costs could be offset by savings in the cost of biologic therapies. Scenario analyses confirmed robustness of results and clinical case scenarios explored cost-effectiveness of potential long-term clinical effects on asthma control, exacerbations, and introduction of biosimilars.

Several studies have been conducted to evaluate the clinical effects of digital inhalers in asthma, but none reported on their cost-effectiveness.[11-15,35] Therefore, it is difficult to compare the results we found for the INCA Sun intervention[16] to other studies involving digital inhaler–based adherence-enhancing strategies. The only previous model-based analysis of a general adherence-enhancing management strategy in asthma was not based on an actual trial, but applied a theoretical intervention. Notably, this study estimated intervention cost-effectiveness at $24,515/QALY (2011 U.S. dollars) from a payer's perspective

and as cost saving from a societal perspective, yet this study was performed before the introduction of biologics and digital inhalers.[28] Comparing the annual usual care costs (excluding biologics) in our model (€3,345, i.e. $3,522) to costs found for severe asthma in the United Kingdom resulted in similar figures. In this U.K. study, annual mean treatment costs in 2011 were between £2,912 and £4,217 (corresponding to current costs between €4,368 and €6,326 with an exchange rate for 2011 of 1.1527 and a Harmonized Index of Consumer Prices [HICP] of 94.32 in 2011 and 122.74 in July 2022) for patients with severe refractory asthma and between £1,670 and £2,788 (corresponding to current costs between €2,505 [$2,638] and €4,182 [$4,404]) for patients with difficult-to-treat asthma, excluding costs for biologic therapies.[36] A Dutch study evaluated the cost-effectiveness of the biologic omalizumab for uncontrolled asthma and found that undiscounted lifetime costs for usual care in patients with severe asthma not using biologics were €215,344 ($226,757) (converted to July 2022 euros, HICP 92.05 in 2010) compared with €87,846 ($92,502) calculated in our model.[37] This difference could be explained by the assumption that resource use for exacerbations was not dependent on the type of exacerbation (ie, same costs used for community-treated, ED-treated, and hospital-treated exacerbations) used in the Dutch study, and by different annual exacerbation rates (3.39 compared with 1.97) in our model. The difference in exacerbation rates is most likely a result of different study designs (ie, the INCA study[16] is a closely monitored prospective clinical trial, whereas the Dutch study[37] calculated usual care costs using retrospective data) and different patient populations (severe vs difficult-to-treat asthma).

Until now, the evaluation of cost-effectiveness of digital inhaler adherence-enhancing strategies in asthma has been an unmet need, hampering real-world implementation of digital inhalers. The model described in this study is the first cost-effectiveness model for evaluation of asthma management to include real-world medication adherence rates in combination with the use of biologic therapies that enables researchers to assess the true value of digital adherence-enhancing interventions. Another strength of this study is that the AdViSHE tool was used to guide validation during the modelling process.

This study has several limitations. First, owing to limited data on absenteeism associated with the different exacerbation types, and on the association between having controlled disease and productivity loss, it was necessary to incorporate some assumptions in the model. Assumptions were, however, well-considered and discussed with experts to ensure minimal uncertainty. Also, we verified the assumption on work absence with the original Work Productivity and Activity Impairment questionnaire data of the INCA Sun dataset[16] and found a trend consistent with the assumption made (ie, a large difference in the level of presenteeism and absenteeism between controlled and uncontrolled patients). The assumptions did not influence the absolute cost difference found between the intervention and the usual care groups because no difference between asthma control status and number of exacerbations was modelled.

A second limitation is the uncertainty regarding long-term costs and effects. No studies have yet been conducted on the long-term effects of digital inhalers, and studies to date have not shown consistent results regarding effects on clinical outcomes, such as improved asthma control. Also, the data used were collected in an experimental randomized controlled trial setting, whereas, preferably, real-world data are used for a long-term cost-effectiveness analysis. In addition, digital inhaler developments are evolving fast, making it difficult to predict the reliability of long-term results. Long-term results were included, given that health economic guidelines require this. Third, the assumption that medication adherence and biologic use would remain stable over time was made, whereas, in real-life, it may fluctuate.[38] Assumptions were also made about the decrease in medication adherence and the increase in biologic use to usual care level after the intervention was stopped. However, these were conservative assumptions because it is likely that a (small) subset of patients will remain more adherent to their therapy after the intervention has stopped. Finally, another potential limitation is that we did not incorporate the economic implication of comorbidities, although these costs are relatively low in comparison with biologics costs.[39]

Before reimbursement and wider-scale implementation of digital inhalers, evidence on their cost-effectiveness is critical. The INCA Sun trial[16] showed that add-on biologics can be reduced for patients with difficult-to-treat asthma when medication adherence and inhaler technique are optimized. In addition, a qualitative study showed that patients with asthma found use of a digital inhaler that provides adherence feedback acceptable and useful.[40] Therefore, policy makers should consider reimbursing digital inhalers for this subgroup of patients comprising approximately ± 15% of the asthma population.[41] Future adaptations of digital inhalers should focus on further personalization of monitoring and interventions.[8] Moreover, real-life effectiveness and cost-effectiveness data are needed for subgroups beyond difficult-to-treat asthma.

In conclusion, we demonstrated the long-term cost-effectiveness of digital inhalers in patients with difficult-to-treat asthma, mostly driven by a lower proportion of patients needing add-on biologic therapy.

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Data and model are available on reasonable request.

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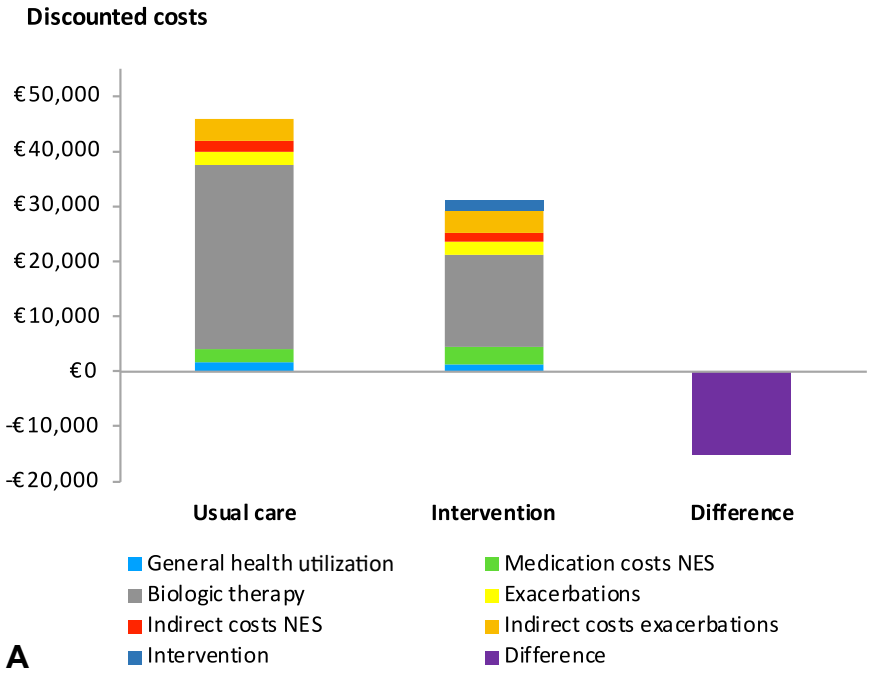


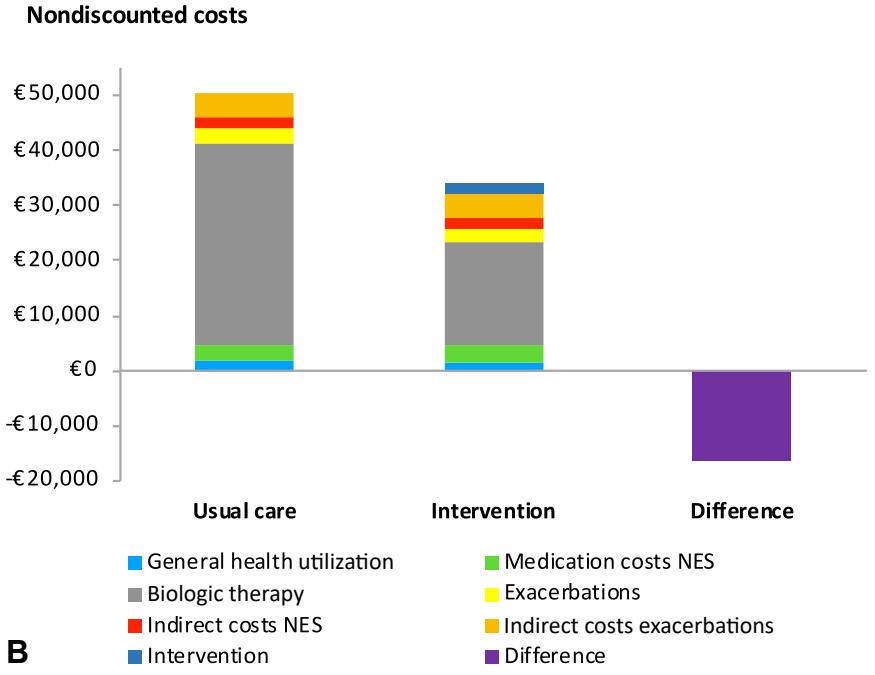
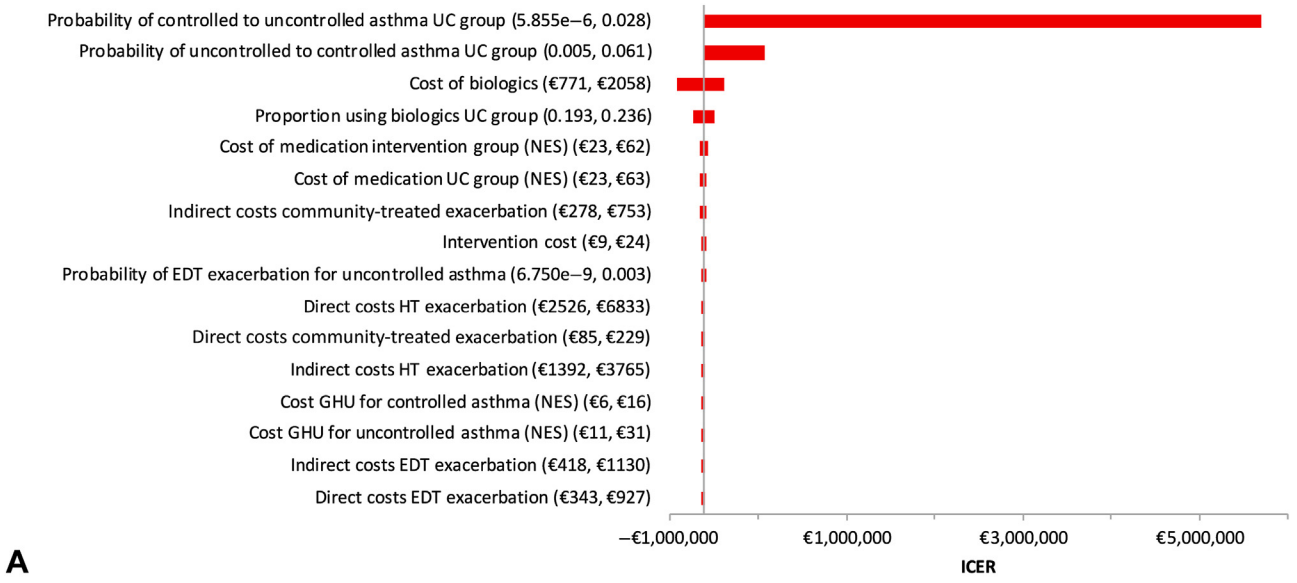


FIGURE E1. The 5-y total costs per patient for INCA (Inhaler Compliance Assessment) Sun intervention and usual care from a societal perspective with a 5-y intervention period. (**A**) Discounted costs. Usual care: general health utilization (€1,556 [$1,638]); medications costs NES (€2,518 [$2,651]); biologic therapy (€33,615 [$35,397]); exacerbations (€2,374 [$2,500]); indirect costs NES (€1,840 [$1,938]); indirect costs exacerbations (€4,085 [$4,302]); intervention (0); and total costs (€45,988 [$48,425]). Intervention: general health utilization (€1,556 [$1,638]); medications costs NES (€2,859 [$3,011]); biologic therapy (€16,917 [$17,814]); exacerbations (€2,374 [$2,500]); indirect costs NES (€1,840 [$1,938]); indirect costs exacerbations (€4,085 [$4,302]); intervention (€1,808 [$1,904]); and total costs (€31,440 [$33,106]). Difference total costs (−€14,548 [−$15,319]). (**B**) Nondiscounted costs. Usual care: general health utilization (€1,695 [$1,785]); medications costs NES (€2,764 [$2,910]); biologic therapy (€36,888 [$38,843]); exacerbations (€2,595 [$2,733]); indirect costs NES (€1,958 [$2,062]); indirect costs exacerbations (€4,462 [$4,698]); intervention (0); and total costs (€50,362 [$53,031]). Intervention: general health utilization (€1,695 [$1,785]); medications costs NES (€3,139 [$3,305]); biologic therapy (€18,565 [$19,549]); exacerbations (€2,595 [$2,733]); indirect costs NES (€1,958 [$2,062]); indirect



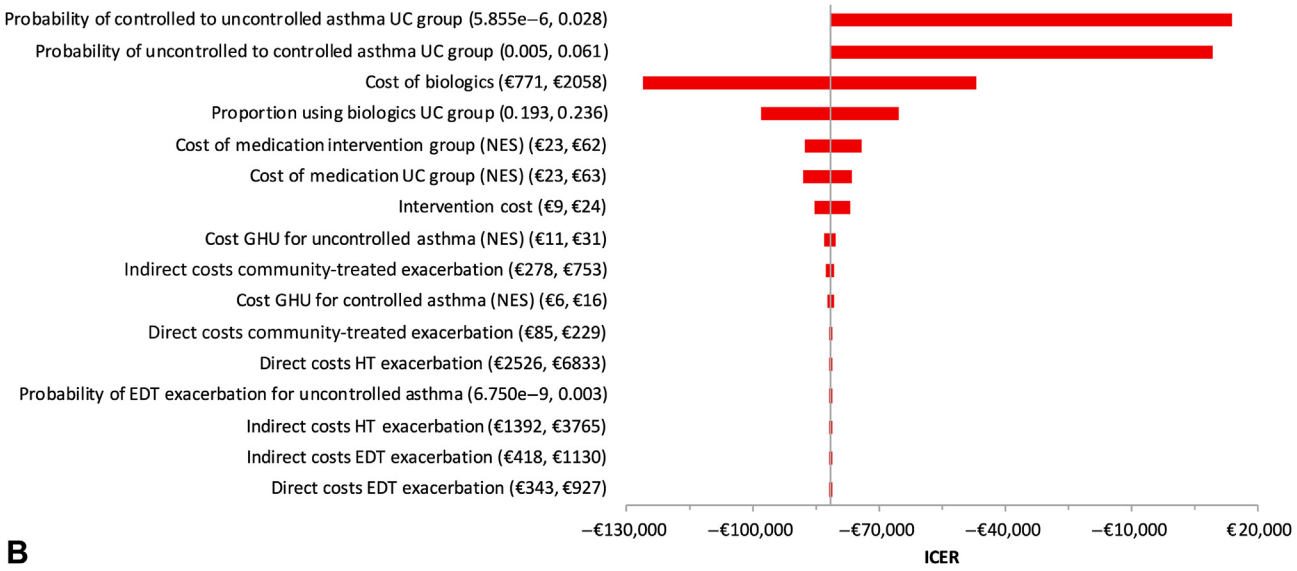
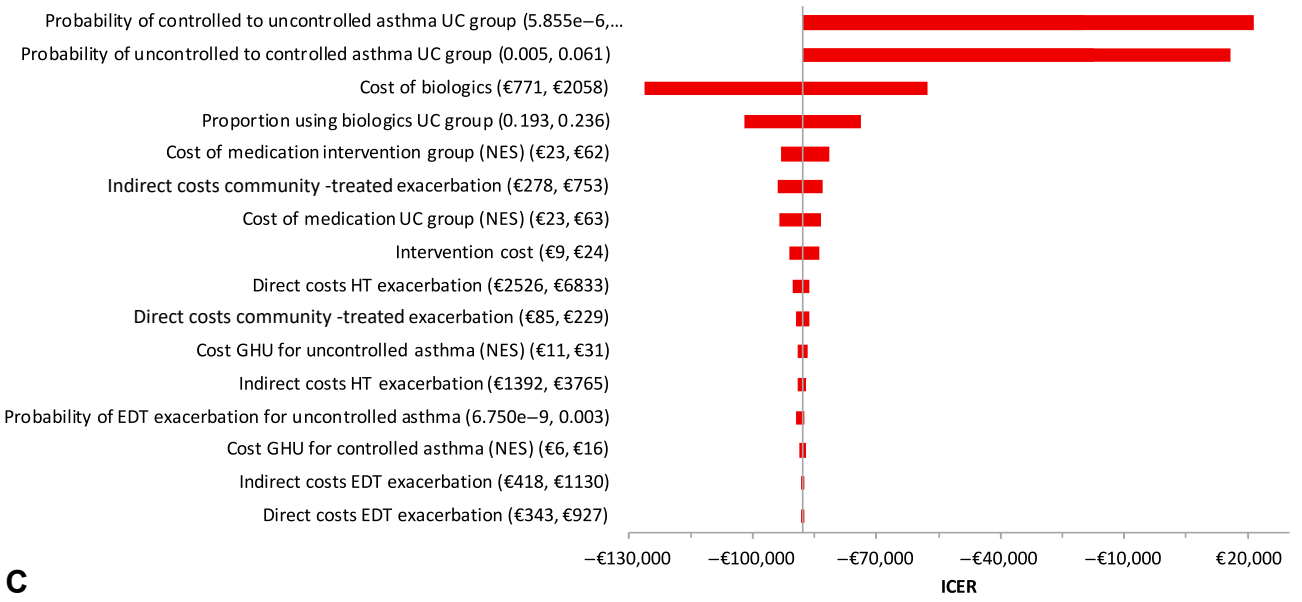


FIGURE E2. Tornado diagram of 1-way sensitivity analyses on ICER for clinical case scenarios 1, 3, and 5. (**A**) Scenario 1: 10% reduction in exacerbations for the intervention group after 1 y. (**B**) Scenario 3: improved asthma control for the intervention group after 1 y. (**C**) Scenario 5: combination of scenarios 1 and 3. *EDT,* Emergency department–treated; *GHU,* general health utilization; *HT,* hospital-treated; *ICER,* incremental cost-effectiveness ratio; *NES,* nonexacerbation state; *UC,* usual care. Values in parentheses refer to the lower and upper interval bounds.

costs exacerbations (€4,462 [$4,698]); intervention (€1,984 [$2,089]); and total costs (€34,398 [$36,221]). Difference total costs (−€15,964 [−$16,810]). *NES,* Nonexacerbation state.



C

FIGURE E2. Continued

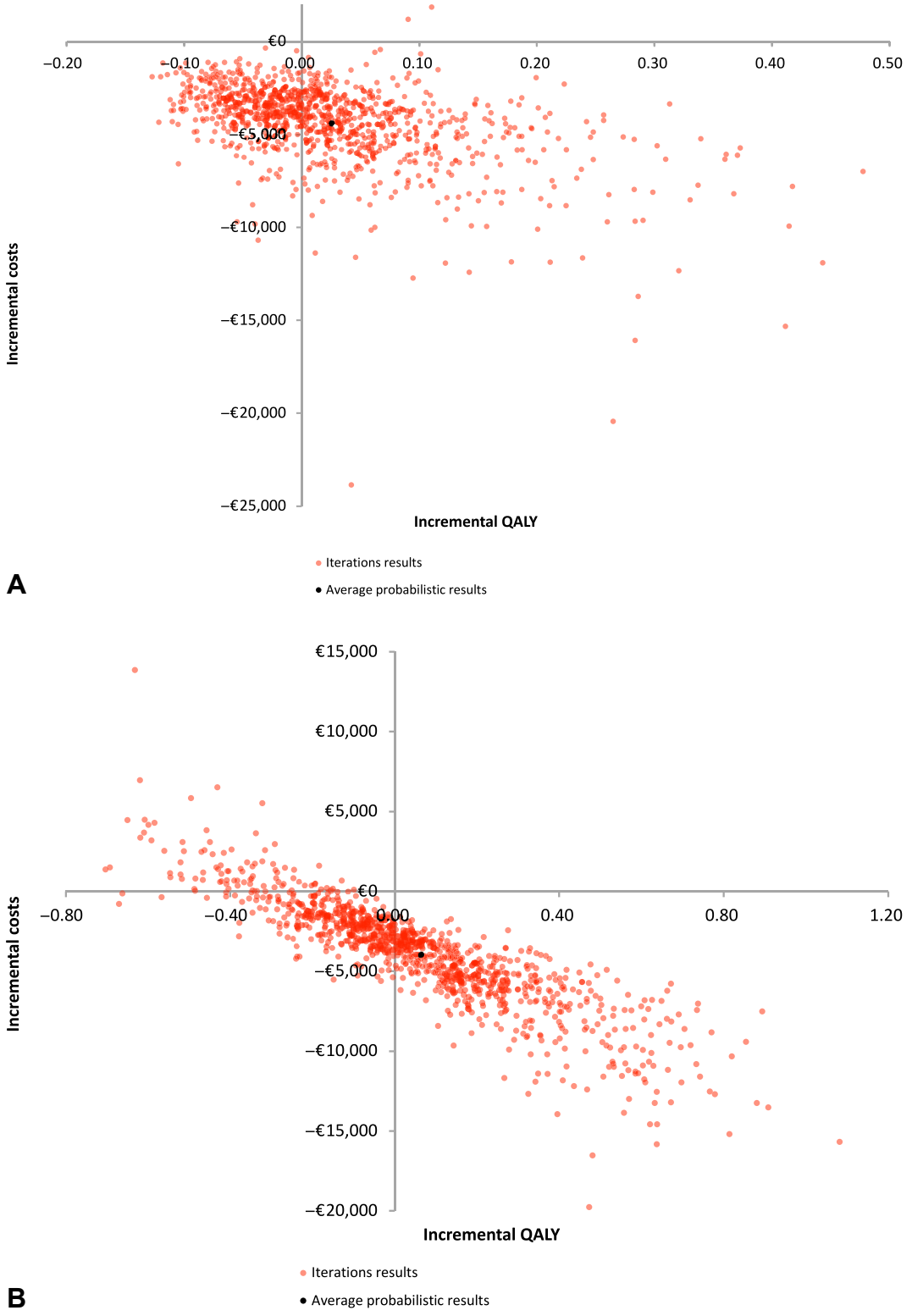


FIGURE E3. Probability sensitivity analysis scatterplots of the incremental costs and QALY for clinical case scenarios 1, 3, and 5. (**A**) Scenario 1: 10% reduction in exacerbations for the intervention group after 1 y. Distribution of iterations over the quadrants: 0.2% Northeast, 0.0% Northwest, 54.4% Southeast, 45.4% Southwest. Average probabilistic outcomes: Usual care: total costs €82,983 ($87,381), QALY 8.057; Intervention: total costs €78,596 ($82,762), QALY 8.083; Difference between usual care in intervention: total costs −€4,386 (−$4,618), QALY 0.026; ICER cost-saving. (**B**) Scenario 3: improved asthma control for intervention group after 1 y. Distribution of iterations over the quadrants: 0.0% Northeast, 9.1% Northwest, 57.4% Southeast, 33.5% Southwest. Average

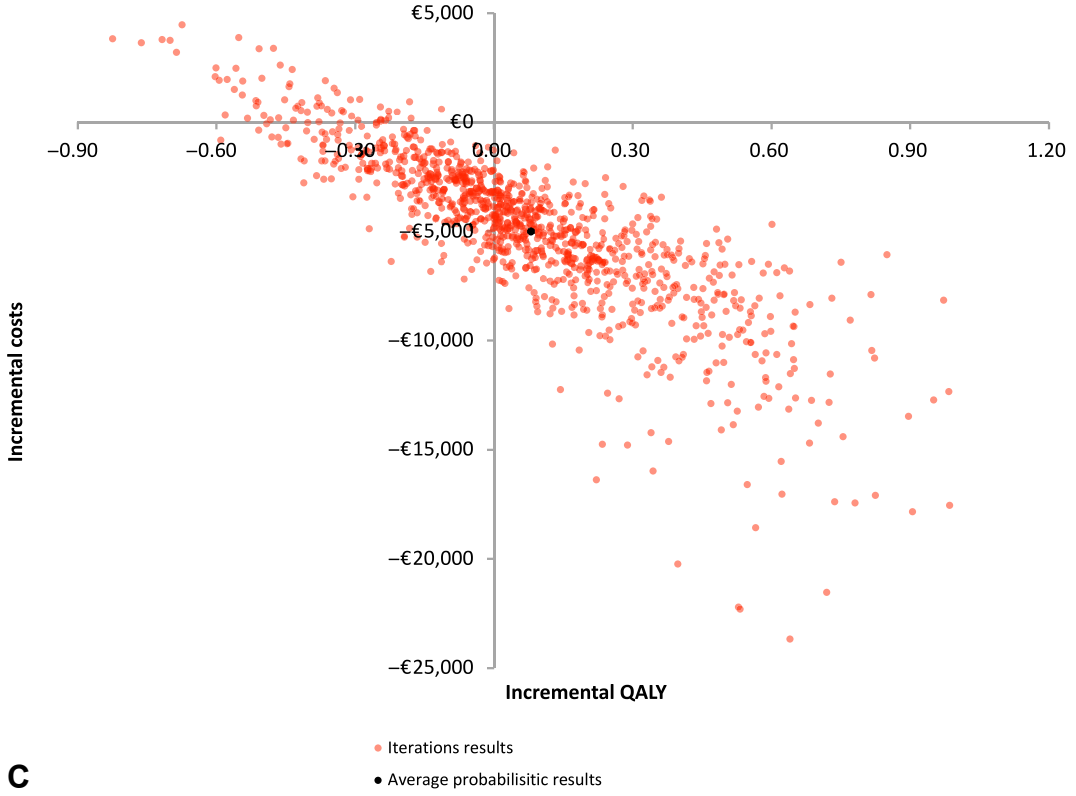


FIGURE E3. Continued

probabilistic outcomes: Usual care: total costs €82,785 ($87,173), QALY 8.051; Intervention: total costs €78,830 ($83,008), QALY 8.115; Difference between usual care in intervention: total costs -€3,955 (−$4,165), QALY 0.064; ICER cost-saving. (**C**) Scenario 5: combination of scenarios 1 and 3. Distribution of iterations over the quadrants: 0.0% Northeast, 6.3% Northwest, 60.3% Southeast, 33.4% Southwest. Average probabilistic outcomes: Usual care: total costs €83,527 ($87,954), QALY 8.038; Intervention: total costs €78,498 ($82,658), QALY 8.118; Difference between usual care in intervention: total costs −€5,029 (−$5,296), QALY 0.080; ICER cost-saving. *QALY,* Quality-adjusted life years; *ICER,* incremental cost-effectiveness ratio.

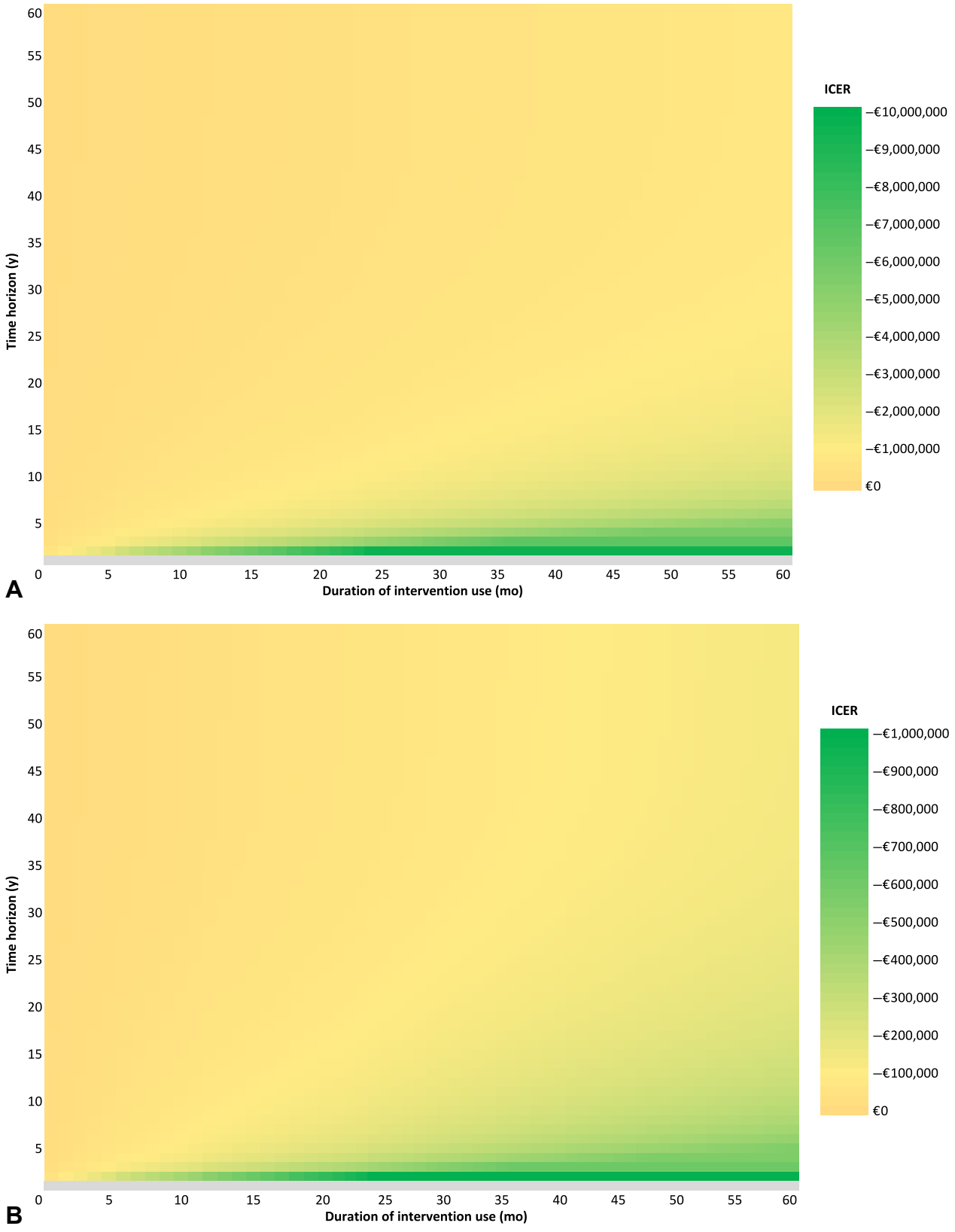


FIGURE E4. Scenario analyses on time horizon and duration of treatment for clinical case scenarios 1, 3, and 5. (**A**) Scenario 1: 10% reduction in exacerbations for the intervention group after 1 y. (**B**) Scenario 3: improved asthma control for intervention group after 1 y. (**C**) Scenario 5: combination of scenarios 1 and 3.

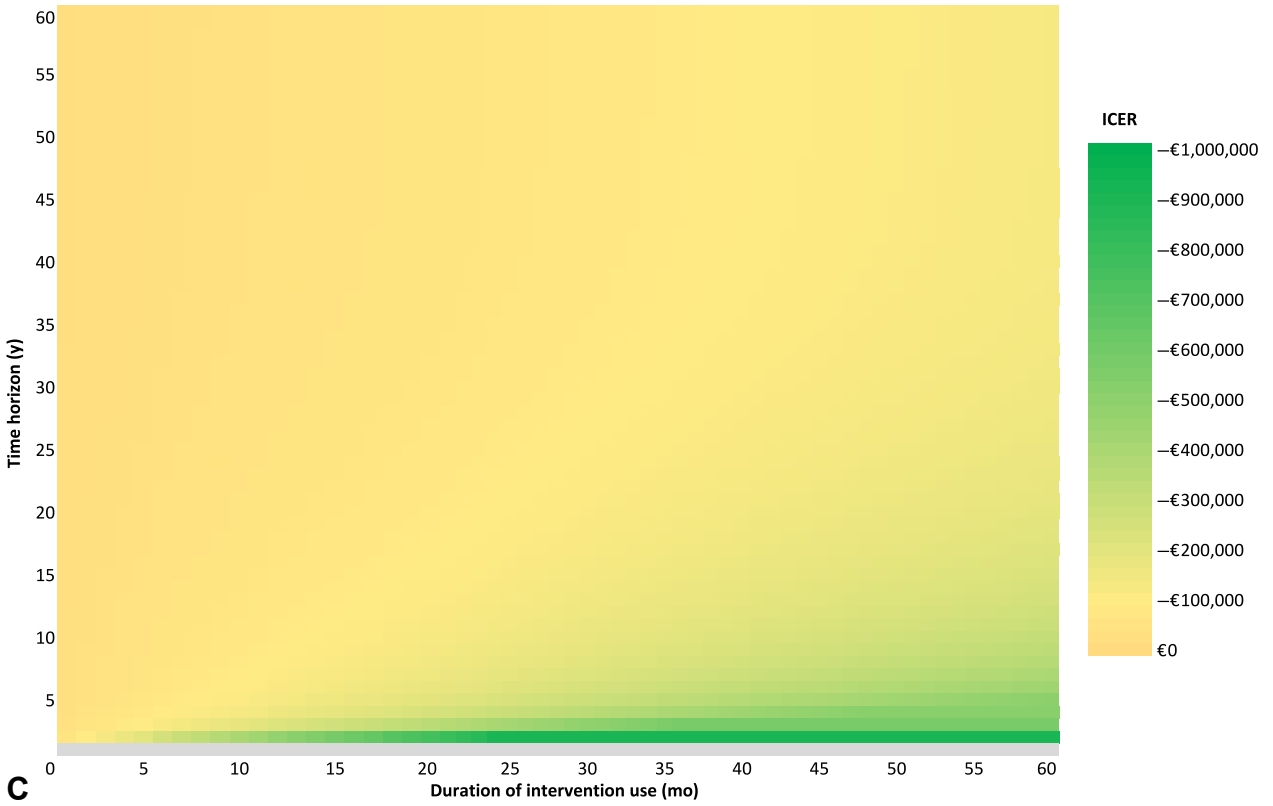


FIGURE E4. Continued

TABLE E1. CHEERS 2022 Checklist

Topic	n	Item	Location where item is reported
Title	1	Identify the study as an economic evaluation and specify the interventions being compared.	1
Abstract	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	4
Introduction			
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	7
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	8
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	8
Setting and location	6	Provide relevant contextual information that may influence findings.	8
Comparators	7	Describe the interventions or strategies being compared and why chosen.	8
Perspective	8	State the perspective(s) adopted by the study and why chosen.	9
Time horizon	9	State the time horizon for the study and why appropriate.	9, 10
Discount rate	10	Report the discount rate(s) and reason chosen.	10
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	10
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	10
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	10, 11
Measurement and valuation of resources and costs	14	Describe how costs were valued.	10, 11
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	11
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	11, 12
Analytics and assumptions	17	Describe any methods for analyzing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	12
Characterizing heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	13, 14
Characterizing distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	13, 14
Characterizing uncertainty	20	Describe methods to characterize any sources of uncertainty in the analysis.	13, 14
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	12
Results			
Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	15
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarize them in the most appropriate overall measure.	15
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	16
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	12
Discussion			
Study findings, limitations, generalizability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	18–21
Other relevant information			

(continued)

TABLE E1. *(Continued)*

Topic	n	Item	Location where item is reported
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	1
Conflicts of interest	28	Report authors' conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	1

CHEERS, Consolidated Health Economic Evaluation Reporting Standards.
From Husereau D, Drummond M, Augustovski F, de Bakker-Grob E, Briggs AH, Carswell C, et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Explanation and Elaboration: a report of the ISPOR CHEERS II Good Practices Task Force. Value Health 2022;25:10-31.

ADVISHE: ASSESSMENT OF THE VALIDATION STATUS OF HEALTH-ECONOMIC DECISION MODELS

Assessment of the Validation Status of Health-Economic decision models (AdViSHE) is a questionnaire that modelers can complete to report on the efforts performed to improve the validation status of their health-economic (HE) decision model. It is not intended to replace validation by model users but rather to inform the direction of validation efforts and to provide a baseline for replication of the results. In addition to using it after a model is finished, the modelers can use AdViSHE to guide validation efforts during the modelling process.

The modelers are asked to comment on the validation efforts performed while building the underlying HE decision model and afterward. Many of the questions simply refer to the model documentation. The AdViSHE is divided into 5 parts, each covering an aspect of validation:

- Part A: Validation of the conceptual model (2 questions)
- Part B: Input data validation (2 questions)
- Part C: Validation of the computerized model (4 questions)
- Part D: Operational validation (4 questions)
- Part E: Other validation techniques (1 question)

No final validation score is calculated because the assessment of the answers and the overall validation effort are left to the model users. It is assumed that the model has been built according to prevailing modelling and reporting guidelines. For instance, the model builders would presumably adhere to the ISPOR-SMDM (International Society for Pharmacoeconomics and Outcomes Research—Society for Medical Decision-Making) Modeling Good Research Practices (Caro et al, 2012)[E1] and/or CHEERS (Consolidated Health Economic Evaluation Reporting Standards) Statement (Husereau et al, 2013).[E2] Some questions may not be applicable to a particular model. If this is the case, the model builder should take the opt-out option and provide a justification of why this item is not deemed applicable.

Part A: Validation of the conceptual model (2 questions)

Part A discusses techniques for validating the conceptual model. A conceptual model describes the underlying system (eg, progression of disease) using a mathematical, logical, verbal, or graphical representation. Please indicate where the conceptual model and its underlying assumptions are described and justified.

The conceptual model is described in the model file (tab M. Structure), as are the underlying assumptions (tab M. Assumptions). The conceptual model and the underlying assumptions are also described in the Methods section of the manuscript.

A1/ Face validity testing (conceptual model): Have experts been asked to judge the appropriateness of the conceptual model?
If yes, please provide information on the following aspects:
- Who are these experts?
- What is your justification for considering them experts?
- To what extent do they agree that the conceptual model is appropriate?

If no, please indicate why not.

Yes, namely:
- Professor H. A. M. Kerstjens, pulmonologist
- Dr. M. van den Berge, pulmonologist
- Dr. F. van Gemert, general practitioner

Justification for these experts: general practitioners and pulmonologists have knowledge about asthma, and are aware of the different disease stages, the heterogeneity of asthma, and health utilization related to asthma. Furthermore, they have knowledge on what usual care comprises.
Agreement regarding appropriateness of conceptual model: we organized a meeting in which we discussed the model in detail. The experts agreed with the disease stages, but a few changes are made regarding input (see part B).

Aspects to judge include appropriateness to represent the underlying clinical process/disease (eg, disease stages, physiological processes); and appropriateness for economic evaluation (eg, comparators, perspective, costs covered).

A2/ Cross validity testing (conceptual model): Has this model been compared with other conceptual models found in the literature or clinical textbooks?
If yes, please indicate where this comparison is reported.
If no, please indicate why not.

Yes, we compared the model to the asthma policy model (Paltiel et al.)[E3] and the model by Zafari et al.[E4] The disease states are overlapping, but we have chosen to omit the partially controlled state and to include 2 states for exacerbation (ie, controlled exacerbation and uncontrolled exacerbation), to be able to apply different transition probabilities for exacerbations in controlled versus uncontrolled patients. Furthermore, our model incorporates adherence level and biologics use, and considers digital adherence enhancing strategies (eg, smart inhalers) as intervention.

Part B: Input data validation (2 questions)

Part B discusses techniques to validate the data serving as input in the model. These techniques are applicable to all types of models commonly used in HE modelling.

Please indicate where the description and justification of the following aspects are given:

- Search strategy
- Data sources, including descriptive statistics
- Reasons for inclusion of these data sources
- Reasons for exclusion of other available data sources
- Assumptions that have been made to assign values to parameters for which no data were available;
- Distributions and parameters to represent uncertainty
- Data adjustments: mathematical transformations (eg, logarithms, squares); treatment of outliers; treatment of missing data; data synthesis (indirect treatment comparison, network meta-analysis); calibration; and the like

Data sources and distributions and parameters to represent uncertainty can be found in the model file:
- Costs: tab I. Econ and appendix tab A. Cost.
- Utility: tab I. Human
- Transition probabilities: tab I. Clinical and appendix tab A. pr

We've included the INCA (Inhaler Compliance Assessment) Sun data where possible, and data sources that fit the model best when data were not available from the INCA Sun study (comparable group of adult patients with asthma).[E5] When assumptions were made because no data were available, this is indicated in the source (or "ref") columns in yellow. For the costs, description of data and assumptions we made are described in the appendix tabs (ie, A. cost (med), A. cost (visits), A. cost (WA), A. cost (Incap)).
Transition probabilities and utility parameters were assigned a beta distribution, which were generated from reported measures of sampling uncertainty (eg, standard errors and confidence intervals). When such measures were not available, expert opinion was used to assign a plausible distribution. Cost parameters were assigned with a gamma distribution, based on a uniform distribution around ±25% of the original cost parameter value.

B1/ Face validity testing (input data): Have experts been asked to judge the appropriateness of the input data?
If yes, please provide information on the following aspects:
- Who are these experts?
- What is your justification for considering them experts?
- To what extent do they agree that appropriate data has been used?

If no, please indicate why not.

Yes, namely:
- Professor H. A. M. Kerstjens, MD, PhD, pulmonologist
- M. van den Berge, MD, PhD, pulmonologist
- F. van Gemert, MD, PhD, general practitioner

Justification for these experts: H. A. M. Kerstjens, M van den Berge, and F. van Gemert work in asthma research and are clinicians that treat asthma patients on daily basis. They know which data sources are available and are aware of factors that could introduce bias. Furthermore, they are able to judge the assumptions we made regarding health utilization and the generalizability of the model.
Agreement regarding appropriateness of conceptual mode: we organized a meeting in which we discussed the model in detail. The experts agreed with data we used as input for the model, but did point out an alternative data source for the asthma-related mortality rate and provided help with estimating volumes of health utilization in case no cost data was available.

Aspects to judge may include but are not limited to potential for bias; generalizability to the target population; availability of alternative data sources; any adjustments made to the data.

B2/ Model fit testing: When input parameters are based on regression models, have statistical tests been performed?
If yes, please indicate where the description, the justification and the outcomes of these tests are reported.
If no, please indicate why not.

Not available.

Examples of regression models include but are not limited to disease progression based on survival curves; risk profiles using regression analysis on a cohort; local cost estimates based on multilevel models; meta-regression; quality-of-life weights estimated using discrete choice analysis; mapping of disease-specific quality-of-life weights to utility values.
Examples of tests include but are not limited to comparing model fit parameters (R^2, Akaike information criterion [AIC], Bayesian information criterion [BIC]); comparing alternative model specifications (covariates, distributional assumptions); comparing alternative distributions for survival curves (Weibull, lognormal, logit); testing the numerical stability of the outcomes (sufficient number of iterations); testing the convergence of the regression model; visually testing model fit and/or regression residuals.

Part C: Validation of the computerized model (4 questions)

Part C discusses various techniques for validating the model as it is implemented in a software program. If there are any differences between the conceptual model (part A) and the final computerized model, please indicate where these differences are reported and justified.

Not available.

C1/ External review: Has the computerized model been examined by modelling experts?
If yes, please provide information on the following aspects:
- Who are these experts?
- What is your justification for considering them experts?
- Can these experts be qualified as independent?
- Please indicate where the results of this review are reported, including a discussion of any unresolved issues.

If no, please indicate why not.

Yes, namely:
- T. L. Feenstra, PhD, associate professor economic evaluation of precision medicine
- L. de Jong, PharmD, PhD, postdoctoral researcher in health economics

Justification for these experts: both experts are working in the field of health economics and have built health economic models. They are familiar with the various techniques and with validation of models. The experts were not involved in the design of the model and were working for different companies or departments than the developers of the model, and are therefore considered independent.
The experts provided advice on the distributions chosen (eg, beta distribution for utilities instead of normal distribution) and on the code structures (ie, simplifying some codes). Furthermore, they advised to use uncertainty for the costs by using a percentage (because of a lack of data on uncertainty), and they pointed out a wrong formula for the calculation of death rate, which we corrected. There were no unresolved issues.

Aspects to judge may include but are not limited to absence of apparent bugs; logical code structure optimized for speed and accuracy; appropriate translation of the conceptual model.

C2/ Extreme value testing: Has the model been run for specific, extreme sets of parameter values in order to detect any coding errors?
If yes, please indicate where these tests and their outcomes are reported.
If no, please indicate why not.

Yes, the following tests have been performed:
Zero and extremely high mortality; treatment adherence from 0% to 100%; 0 to 1000 euro treatment costs; 0 to 10 exacerbation relative risks; 0% to 100% probability exacerbations; 0 to 1 proportion of patients using biologics; 0 to 1 utilities for each state; 0 to 1 probability for going from controlled to uncontrolled state and *vice versa* for usual care and intervention group; costs of biologics were varied from 0 to 10000 euros.

Examples include but are not limited to 0 and extremely high (background) mortality; extremely beneficial, extremely detrimental, or no treatment effect; 0 or extremely high treatment or health care costs.

C3/ Testing of traces: Have patients been tracked through the model to determine whether its logic is correct?
If yes, please indicate where these tests and their outcomes are reported.
If no, please indicate why not.

Yes, traces were tested, and outcomes are stored within the model trace tabs (Trace_soc and Trace_TP).

In cohort models, this would involve listing the number of patients in each disease stage at one, several, or all time points (eg, Markov traces). In individual patient simulation models, this would involve following several patients throughout their natural disease progression.

C4/ Unit testing: Have individual submodules of the computerized model been tested?
If yes, please provide information on the following aspects:
- Was a protocol that describes the tests, criteria, and acceptance norms defined beforehand?
- Please indicate where these tests and their outcomes are reported.
If no, please indicate why not.

Yes. Protocol for unit testing are defined as turning on and off and altering global parameters in the model setting tab; each formula and macro are specifically tested for sensitivity and scenario analyses.

Examples include but are not limited to turning submodules of the program on and off; altering global parameters; testing messages (eg, warning against illegal or illogical inputs), drop-down menus, named areas, switches, labelling, formulas and macros; removing redundant elements.

Part D: Operational validation (4 questions)

Part D discusses techniques used to validate the model outcomes.

D1/ Face validity testing (model outcomes): Have experts been asked to judge the appropriateness of the model outcomes?
If yes, please provide information on the following aspects:
- Who are these experts?
- What is your justification for considering them experts?
- To what extent did they conclude that the model outcomes are reasonable?
If no, please indicate why not.

Yes, the clinical experts as described under A1 and the modelling experts as described under C1 were asked to judge the model outcomes. The clinicians have knowledge of what are informative outcomes for asthma specific, whereas the modelling experts have knowledge on outcomes that can be used to compare cost-effectiveness across disease areas (eg, incremental cost-effectiveness ratio [ICER]). Both groups of experts considered the proposed outcomes to be reasonable.

Outcomes may include but are not limited to:(quality-adjusted) life years; deaths; hospitalizations; total costs.

D2/ Cross validation testing (model outcomes): Have the model outcomes been compared with the outcomes of other models that address similar problems?
If yes, please provide information on the following aspects:
- Are these comparisons based on published outcomes only, or did you have access to the alternative model?
- Can the differences in outcomes between your model and other models be explained?
- Please indicate where this comparison is reported, including a discussion of the comparability with your model.
If no, please indicate why not.

No, because no models are available that address similar problems. The model of Zafari et al.[E4] is the model that is the most comparable; however, in that model digital inhalers are not considered, and the use of biologics is not included.

Other models may include models that describe the same disease, the same intervention, and/or the same population.

D3/ Validation against outcomes using alternative input data: Have the model outcomes been compared with the outcomes obtained when using alternative input data?
If yes, please indicate where these tests and their outcomes are reported.
If no, please indicate why not.

We used different literature sources as alternative input data to perform 4 clinical case scenarios as described in the manuscript (eg, probabilities for controlled to uncontrolled asthma and *vice versa* from the randomized controlled trial [RCT] by Merchant et al, 2016[E6]), reduction in exacerbations, reduction in cost of biologics based on previous biosimilar introduction in other disease areas). Outcomes are reported in the manuscript and Online Repository material.

Alternative input data can be obtained by using different literature sources or datasets, but can also be constructed by splitting the original dataset in 2 parts, and using one part to calculate the model outcomes and the other part to validate against.

D4/ Validation against empirical data: Have the model outcomes been compared with empirical data?
If yes, please provide information on the following aspects:
- Are these comparisons based on summary statistics, or patient-level datasets?
- Have you been able to explain any difference between the model outcomes and empirical data?
- Please indicate where this comparison is reported.

If no, please indicate why not.
D4.A/ Comparison against the data sources on which the model is based (dependent validation).

Yes, we compared the model outcomes to the costs and number of exacerbations as described in the INCA Sun study paper.[E5] The results are reported in Table E1). Furthermore, we compared the model outcomes with the other data sources the model is based on, see following table.

Parameter	Outcome model after 1 y (calculated in trace_tabs, cycle 1 −26)	Reference	Outcome reference	Remarks
ED treated exacerbations in 1 y	UC: 1.04% INT: 1.04%	Honkoop et al[E7]	Partially controlled group: 3 of 219 (1.37%) Total: 8 of 611 (1.31%)	Controlled and uncontrolled patients were included.
Number of controlled and uncontrolled patients	UC: 73% controlled INT: 73% controlled	Merchant et al[E6]	After 1 y: Initially uncontrolled adults: UC 49% controlled; INT: 63% controlled. Whole population: UC 69% controlled; INT 72% controlled	Controlled and uncontrolled patients were included.
Asthma-related death in 1 y	UC: 0.045% INT: 0.045%	RIVM (vzinfo.nl)	171 deaths, 636,200 patients of which 45% is uncontrolled (assumption based on literature) → 171/(0.45*636200) = 0.060%	Data 2018 not available anymore on www.vzinfo.nl (updated to 2021), but it is available in the model (tab A. pr)
RR of exacerbations for uncontrolled patients vs controlled patients	Checked for 3 cycles when scenario 1 is turned on (improvement in asthma control in INT group): cycle 20: CT 1.60, EDT 2.38, HT 1.37; cycle 100: CT 1.52, EDT 2.26, HT 1.30; cycle 500: CT 1.51, EDT 2.25, HT 1.30.	Sullivan et al[E8]	Community treated: 1.510 ED treated: 2.310 Hospital treated: 1.330	Because no difference in control status exists between UC group and INT group, this RRs cannot be checked for the model when the scenarios are turned off.

CT, Community treated; *ED,* emergency department; *EDT,* emergency department treated; *HT,* hospital treated; *INT,* intervention; *RR,* risk ratio; UC, usual care;

D4.B/ Comparison against a data source that was not used to build the model (independent validation).

We have compared the model outcomes where possible with studies that evaluated use of digital inhalers on exacerbations, medication adherence levels, and costs. However, costs were not reported in these studies.

General remarks:
- Merchant et al[E6]: focuses on short-acting β-agonist (SABA) use, not on preventer inhaler use
- Foster et al[E9]: population does not have severe asthma.
- Hoyte et al[E10]: focuses on SABA use, not on preventer inhaler use, short study of 12 wk

Exacerbations
- Merchant et al[E6]: not reported
- Foster et al[E9]: no difference in exacerbations between intervention and control group.
- Moore et al[E11]: 4 exacerbations reported, 2 in arm 1, 1 in arm 2 and 1 in arm 5 (control group), no statistical difference between groups.
- Kuipers et al[E12]: no difference in exacerbations between the group that used electronic monitoring and the group that did not use electronic monitoring.
- Hoyte et al[E10]: no difference in exacerbations between intervention and control group.

Medication adherence levels
- Merchant et al[E6]: only measured SABA use, not preventer use.
- Foster et al[E9]: adherence rate in intervention 73% and control group 46% (compared with 65% and 55% in INCA Sun/model).
- Moore et al[E11]: adherence rate in intervention 82% and control group 71% (compared with 65% and 55% in INCA Sun/model).
- Kuipers et al[E12]: 4.52-fold increase in group that used electronic monitoring (actual rates not given).
- Hoyte et al[E10]: only measured SABA use, not preventer use.

Costs
- Merchant et al[E6]: not reported
- Foster et al[E9]: not reported
- Moore et al[E11]: not reported
- Kuipers et al[E12]: not reported
- Hoyte et al[E10]: not reported

Part E: Other validation techniques (1 question)

E1/ Other validation techniques: Have any other validation techniques been performed?
If yes, indicate where the application and outcomes are reported, or else provide a short summary here.

We have organized 2 walk-throughs: 1 with clinicians and 1 with modelers as described under sections A and C.

Examples of other validation techniques: structured walk-throughs (guiding others through the conceptual model or computerized program step-by-step); naive benchmarking (back-of-the-envelope calculations); heterogeneity tests; double programming (2 model developers program components independently and/or the model is programmed in 2 different software packages to determine whether the same results are obtained).

TABLE E3. Scenario analyses based on clinical cases from a societal perspective with an intervention duration of 1 y and a time horizon of 5 y

Outcome parameter	Usual care	Intervention	Difference
Scenario 1 (10% reduction in exacerbations in intervention group after 1 y)			
Total costs (euros [U.S. dollars])	45,988 (48,425)	42,331 (44,575)	−3,658 (−3,852)
QALY	4.137	4.140	0.003
Number of exacerbations	7.813	7.216	0.597
ICER		Cost-saving	
Scenario 2 (5% reduction in exacerbations in intervention group after 1 y)			
Total costs	45,988 (48,425)	42,556 (44,811)	−3,432 (−3,614)
QALY	4.137	4.138	0.001
Number of exacerbations	7.813	7.514	0.299
ICER		Cost-saving	
Scenario 3 (improved asthma control as found by Merchant et al in intervention group after 1 y)			
Total costs	45,988 (48,425)	42,474 (44,725)	−3,514 (−3,700)
QALY	4.137	4.164	0.027
Number of exacerbations	7.813	7.685	0.128
ICER		Cost-saving	
Scenario 4 (50% of the improvement in asthma control as found by Merchant et al in intervention group after 1 y)			
Total costs	45,988 (48,425)	42,666 (44,927)	−3,322 (−3,498)
QALY	4.137	4.147	0.010
Number of exacerbations	7.813	7.765	0.048
ICER		Cost-saving	
Scenario 5 (improved asthma control and 10% reduction in exacerbations in intervention group after 1 y)			
Total costs	45,988 (48,425)	42,030 (44,258)	−3,958 (−4,168)
QALY	4.137	4.167	0.030
Number of exacerbations	7.813	7.101	0.712
ICER		Cost-saving	
Scenario 6 (biosimilar introduction)			
Total costs	37,584 (39,576)	35,298 (37,169)	−2,287 (−2,408)
QALY	4.137	4.137	0.000
Number of exacerbations	7.813	7.813	0.000
ICER		N/A	

ICER, Incremental cost-effectiveness ratio; *QALY,* Quality-adjusted life years.

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