



The cost-effectiveness of requiring universal vs contextual self-injectable epinephrine autoinjector for allergen immunotherapy

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ABSTRACT

Background: Aeroallergen immunotherapy (AIT) is a safe and effective disease-modifying treatment associated with rare therapy-associated fatality. Significant practice variation surrounds universal or contextual prescription of self-injectable epinephrine (SIE) for patients receiving AIT.

Objective: To characterize the cost-effectiveness of a universal vs contextual SIE requirement for patients receiving AIT.

Methods: An economic evaluation using cohort and microsimulation was performed from both the societal and health care sector perspectives for patients undergoing AIT, assessing a universal requirement to fill SIE prescriptions at the outset of therapy compared with requiring this only after a systemic reaction to immunotherapy (SRIT).

Results: A universal SIE requirement for AIT is not cost-effective, with the incremental cost-effectiveness ratio for this strategy estimated at \$669,327,730 per quality-adjusted life-year (QALY). In the microsimulation ($n = 10,000$), the mean (SD) costs of a universal approach exceeded that of a more context-specific strategy where SIE was only prescribed for patients after an initial SRIT (\$19,653.36 [\$4296.66] vs \$16,232.14 [\$5204.32]), and given the effects on rates of AIT discontinuation, the universal approach was less effective (mean [SD], 25.555 [2.285] QALYs) compared with a contextualized approach (mean [SD], 25.579 [2.345] QALYs). Universal SIE prescription could be cost-effective if it provided a 1000 times protection against AIT fatality at a value-based cost of \$24, and the annual AIT fatality rates unrealistically exceed 2.6 per 10,000 patients.

Conclusion: In a simulation of potential SIE-prescribing strategies for patients receiving AIT, a universal approach to an epinephrine autoinjector requirement was not cost-effective when compared with an approach in which an SIE is prescribed only to patients with prior SRIT.

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Introduction

Allergen immunotherapy (AIT) is a well-established treatment modality with proven disease-modifying efficacy in allergic rhinitis (AR) and/or allergic rhinoconjunctivitis (ARC), as well as efficacy in preventing asthma triggered by seasonal or perennial allergens. Since the sentinel paper published in 1911 by Noon and Freeman¹ describing AIT for grass allergy—associated hay fever, AIT has been the hallmark of the modern allergy practice and is the most identifiable procedure associated with our specialty.² The modern practice of AIT is associated with a high degrees of therapeutic efficacy, as well as quality of care and safety. Since the late 1990s, there have been 3 iterations of detailed practice parameters from the American Academy of Allergy, Asthma, and Immunology (AAAAI) and the American College of Allergy, Asthma, and Immunology (ACAAI) that have established an evidence-based set of recommendations to help guide the practitioner in the office-based practice of providing AIT to inhalants as well as venom-containing stinging and biting insects. AIT has well-known risks of allergic reactions, including potentially severe systemic reactions and fatal anaphylaxis. For this reason, the practice is strictly regulated—specific testing is required, the extract is diluted from its concentrate and built up in a slowly titrated manner over time, and AIT is exclusively prescribed and administered under the supervision and direction of a board-certified allergist/immunologist (or otolaryngologist) trained in the evaluation, management, provision, and supervision of allergen immunotherapy. With the use of nonrush, conventional dosing schedules, systemic reactions to immunotherapy (SRITs) occur with 0.2% of injections and at an overall frequency of approximately 1%.² A retrospective review of 435,854 injections administered to 4600 patients during 20 years (1981–2000) noted a SRIT rate of 5.2% per patient course of immunotherapy during this period, although the SRIT rate was higher in the first 10 years compared with the second 10 years.^{3,4} Variation exists in rates of systemic reactions, with 1 report noting a 4% rate of SRIT during 1 year of treatment.⁵ AIT-related fatalities are rare but occur at a rate of approximately 1 per 2.5 million injections and are attributable to approximately 3.4 deaths per year.⁵

Given the risk of an SRIT, injections are closely monitored, with a recommendation that all patients undergoing AIT are observed for 30 minutes after their injection in the supervising physician's office to assess for development of systemic reactions during this time frame.² While post-injection observation is standard practice, variation exists in the decision to prescribe self-injectable epinephrine (SIE) to all patients undergoing AIT. Per the language of summary statement 36 in the latest (2011) Allergy Joint Task Force practice parameter, “the decision to prescribe epinephrine autoinjectors to patients receiving AIT is up to the physician's discretion and is based on a number of considerations.”⁵ However, this may be a somewhat common practice, and for some offices, this is a prestipulated requirement for any patient to receive immunotherapy, irrespective of their prior reaction history.

Although epinephrine is the unequivocal first-line therapy to treat anaphylaxis, its use is generally geared to prevent anaphylaxis-related morbidity and fatality. Interestingly, multiple recent publications have questioned the cost-effectiveness of practices commonly implemented in the treatment of allergic reactions, and additionally have suggested value-based prices (eg, a medication pricing strategy showing a value for the medication that is cost-effective based on its outcomes) for epinephrine autoinjectors.^{6–10} Given variation in the universal requirement of SIE for patients undergoing AIT, we undertook this analysis to explore the health and economic outcomes of the policy of routinely prescribing SIE for all patients undergoing AIT and

to evaluate under what circumstances such a practice is cost-effective.

Methods

Model Structure

Markov cohort and microsimulation were used to determine the cost-effectiveness of routine SIE prescriptions for all individuals receiving aeroallergen immunotherapy (AIT compared with providing SIE only to individuals with a prior SRIT (TreeAge Pro 2018). Markov modeling allows evaluation of health state transitions and incorporates costs and health state utility variation. The base case scenario was represented by a 5-year-old child with AR receiving a 5-year course of AIT, with or without a routine universal SIE requirement (Fig. 1). The base case was selected to represent the lower limit of age at which AIT would be considered to maximize duration of AIT benefit and the benefit of an SIE protective effect over the model horizon.² All patients experiencing an SRIT were subsequently transitioned to a required SIE strategy. An 80-year time horizon was incorporated to evaluate longer-term benefits of AIT following course completion, with age-adjusted all-cause mortality included in the model.¹¹ Costs, probabilities, and utilities associated with AIT were derived from the literature and listed in Table 1. The analysis followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) reporting guidelines.¹² A health care perspective that included SIE costs was used for the base case analysis with a broader societal perspective inclusive of indirect job-related opportunity costs included in the sensitivity analysis as recommended by the Second Panel on Cost-Effectiveness in Health and Medicine.¹³

Costs

Costs were reported in 2019 dollars with future costs discounted at 3% per year to account for decreased value of costs experienced in the future vs in the present.^{14,15} Annual AIT costs were estimated at \$510 based on a retrospective analysis by Hankin et al.¹⁶ The authors used Florida Medicaid claims data collected from July 1, 1997, to June 30, 2009, to determine AIT cost to the health care system. AIT reduced total health care costs for AR for adults and children by 37.6%.¹⁶ AR costs were derived from Allen-Ramey et al,¹⁷ who evaluated AR costs via retrospective analysis of medical and pharmacy claims from January 2009 to February 2014.

SIE twin-pack annual cost was estimated to be \$659 from previously published reports and commercial costs.¹⁸ Patients who had an anaphylactic reaction that required additional care were assumed to require emergency department (ED) evaluation, with some admitted overnight for observation as per current anaphylaxis management plan recommendation. Clark et al¹⁹ evaluated all causes of anaphylaxis identified in the Thomson Reuters MarketScan Commercial and Medicare Supplemental Database compiling claims records from January 2002 to December 2008 that included detailed cost, health care utilization, and outcomes data. Individuals who presented to the ED or were admitted for anaphylaxis were identified based on *International Classification of Diseases, Ninth Revision* codes. This study found that the cost of anaphylaxis resulting in an ED visit was \$1157 (\$1512 in 2019 dollars) and the cost of hospitalization was \$5653 (\$7388 in 2019 dollars).¹⁹

Probabilities and Events

SRIT were estimated to occur in 4% of patients undergoing AIT annually, with further care in an ED assumed for the 9% of patients with SRIT who had a grade 4 reaction using World Allergy

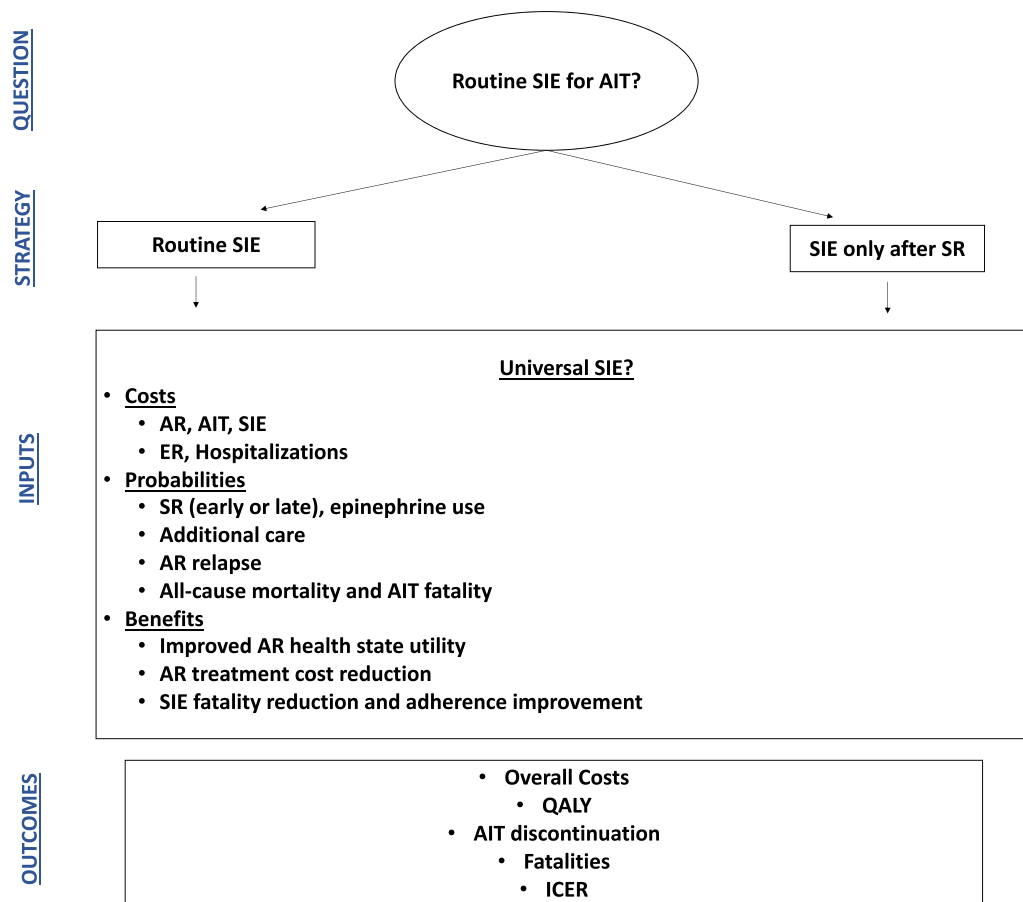


Figure 1. Decision model. Decision analysis of universal vs contextual self-injectable epinephrine (SIE) strategies for aeroallergen immunotherapy. AIT, aeroallergen immunotherapy; AR, allergic rhinitis; ED, emergency department; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SR, systemic reaction.

Organization criteria.⁵ Hospitalization rates for patients evaluated in the ED were derived from Clark et al¹⁹ in which 22% of patients with an ED visit or hospitalization for anaphylaxis were hospitalized for investigator-defined severe anaphylaxis. Rates of SRIT epinephrine treatment and SRIT timing were based on the work of Epstein et al,²⁰ who recently conducted a survey study of members from the ACAAI and AAAAI to evaluate the rate of systemic reactions caused by AIT between 2008 and 2016.^{20,21} In early reactions (<30 minutes), epinephrine was administered in 77% of cases.²⁰ The rate of SIE use for delayed reactions was also based on data from the ACAAI and AAAAI survey, which reported an SIE use rate of 19%.²⁰ Fatal AIT-associated anaphylaxis is a rare event and subject to significant ascertainment bias. Epstein et al²² also evaluated patients who had fatal reactions secondary to AIT, reporting 4 fatalities among 3,279,442 patients during a 6-year period (probability of fatality from AIT of 1.22×10^{-6}). To account for underreporting, this period risk was applied as an annual risk for patients receiving AIT, with sensitivity analyses evaluating this fatality risk during the cumulative course.

Studies evaluating adherence to AIT estimate that rates of completing therapy vary from 23% to 88%.²³ The attrition rate of AIT was estimated by Hsu et al²⁴ via a retrospective review of 217 patients receiving immunotherapy at Weill Cornell Medical College between 2007 and 2010. Analysis evaluated patients who withdrew from AIT and the duration of therapy before withdrawal. The cumulative probability of discontinuing AIT at any time during therapy was 45%. Given the uncertainty surrounding this parameter, in sensitivity analysis, this value was varied across a range of 6% to 84% based on a study by Cox et al²⁵ that compiled and reviewed studies evaluating adherence to AIT.

In patients successfully completing AIT, some will have recurrence of AR symptoms. Lee et al²⁶ conducted a retrospective review of patients completing a course of AIT to house dust mite from 2000 to 2012 and evaluated remission via medical record review using lack of documentation of rhinitis symptoms as an indication of cure and lack of use of maintenance medications (such as intranasal corticosteroids or antihistamines) for at least a year. The overall remission rate in this study was 76.6%. As such, the model incorporated a 23.4% relapse rate spread over the initial 5 years after AIT.

Health State Utilities

In the base case, patients entering the model were assumed to have moderate AR, improving to mild AR with the use of AIT. Given variability in actual severity and AIT improvements, wide sensitivity ranges were included around these inputs. The baseline health state utility of individuals with moderate AR was estimated to be 0.864 with mild AR estimated at 0.880 based on a study by Retzler et al.²⁷ This study surveyed adults and children using health state descriptions with a standard gamble approach for adults and a visual analog scale for children to determine the effect of ARC. The value of 0.864 reflects the baseline health state of adults with moderate ARC. Because values differed between adults and children, this parameter was varied across a range that included the lowest utility of 0.635 (severe ARC with uncontrolled asthma in children) to the highest utility of 0.880 (mild ARC in adults) in sensitivity analyses, which also included additional approaches evaluating health state utility of AR with and without AIT. Health benefits were expressed in quality-adjusted life-years (QALYs).

Table 1
Costs, Probabilities, and Utilities Associated With AIT

Parameter	Value (range)	Reference
Costs (2019 dollars)		
Allergic rhinitis, \$	703 (240–2088)	Allen-Ramey et al, 2017 Hankin et al, 2013
Allergen immunotherapy, \$	510 (439–583)	
AIT cost reduction, %	37.6 (30–42)	Hankin et al, 2013
SIE, \$	659 (110–684)	GoodRx, 2019
ED, \$	1512 (1393–1661)	Clark et al, 2014
Hospitalization, \$	\$7388 (6809–8114)	Clark et al, 2014
Probabilities		
Additional care inclusive of ED care, %	9 (1–30)	Phillips et al, 2011
Hospitalization, %	22 (2–30)	Clark et al, 2014,
SR, %	4 (0.6–34)	Epstein et al, 2019, Cox et al, 2011, Bernstein et al, 2011, Phillips et al, 2011
Proportion of early SR, %	84.5 (50–86)	Epstein et al., 2019, Cox et al, 2011
AIT fatality	0.00000122 (0–0.00001)	Epstein et al, 2016
AIT discontinuation (cumulative), %	45 (6–84)	Cox et al, 2014, Hsu et al, 2012
Epinephrine for SR in clinic, %	77 (71–94)	Epstein et al, 2011
SIE used after clinic discharge, %	19 (8–100)	Epstein et al., 2019
Relapse, %	23.4 (0–55)	Lee et al, 2018, Cox et al, 2011
Utilities and mortality		
Utility mild AR	0.880 (0.864–1)	Retzler et al, 2018
Utility moderate AR	0.864 (0.635–0.88)	Retzler et al, 2018
US mortality table	Age specific	Arias, 2018
SIE fatality risk reduction	10-fold decrease (5-fold to 100-fold decrease)	Estimate

Abbreviations: AIT, allergy immunotherapy; AR, allergic rhinitis; ED, emergency department; SIE, self-injectable epinephrine; SR, systemic reaction.

Sensitivity Analyses

Models evaluated practice variation in AIT discontinuation, either from physician recommendation or patient preference. Although the cohort analysis did not restrict patients from continuing AIT regardless of the number of prior SRITs, patients in the microsimulation discontinued AIT if they experienced 2 SRIT. Because the SIE requirement may variably create a barrier to AIT for some patients, the cohort simulation did not assume SIE had any effect on adherence or discontinuation rate, whereas the microsimulation accounted for less attrition in patients without an SIE requirement by assuming a 75% relative rate of AIT discontinuation. Exploratory analyses were performed using previously published value-based SIE costs,⁹ including an upper limit assumption of 1000 times fatality reduction associated with SIE use, to determine the AIT fatality rate under which universal SIE would be cost-effective. Deterministic and probability sensitivity analyses were performed across ranges shown in Table 1, with probabilistic sensitivity analyses using triangular modal distributions around the base case value. Additional sensitivity analyses were performed using childhood health state utility for moderate AR (0.675) and mild AR (0.705) across the model horizon, as well as separate utility measures for individuals younger than 12 years (moderate AR, 0.675; mild AR, 0.705) and those 12 years and older (moderate AR, 0.864; mild AR, 0.880). Sensitivity analyses were performed through start ages to 60 years of age. Sensitivity analysis explored the effect of additional indirect costs in the cohort and microsimulation from a broader societal perspective by including additional non-SIE-related, job-related opportunity costs, assuming a mean hourly wage of \$27.83, round trip travel time of 1 hour, and clinic administration and observation of 1 hour with 36 visits in year 1 and 12 annual visits in subsequent years.²⁸

Results

Throughout the model, the mean (SD) microsimulation ($n = 10,000$) costs of a universal SIE approach exceeded that of a more context-specific strategy in which SIE was only given for patients after a first SRIT (\$19,653.36 [\$4296.66] vs \$16,232.14 [\$5204.32]). Given the effects on rates of AIT discontinuation, the universal SIE approach was less effective (25.555 [2.285] QALYs) compared with a contextualized approach (25.579 [2.345] QALYs). Given rare fatality, no patient in the microsimulation experienced fatal anaphylaxis, and a universal SIE strategy was dominated (eg, a dominated strategy produces higher costs and lower benefits relative to a comparator) by a contextual approach. The cohort analysis demonstrated similar results, with a universal SIE strategy costing \$669,327,730 per QALY (net monetary benefit [NMB] of universal SIE vs a contextualized approach, \$2,536,724.94 vs \$2,539,324.45). During the microsimulation AIT, premature discontinuations occurred in 54.85% of patients in the universal SIE policy and 44.55% of those in the contextual approach policy, resulting in both greater accumulation of benefit and greater risk for SRITs attributable to greater use of AIT (17.95% for universal SIE vs 19.67% for contextual approach). Because patients required to universally obtain SIE had a greater rate of AIT discontinuation in the microsimulation, this group also had a lower rate of SRIT during the microsimulation (Table 2).

Cost-effectiveness was difficult to obtain with a universal SIE approach; however, if an SIE was able to provide a 1000-fold risk reduction for AIT fatality at a value-based device cost of \$24 per twin pack, this strategy was cost-effective when annual AIT fatality rates reached 2.7 per 10,000 patients (Fig. 2). An additional health state utility sensitivity cohort analysis did not find the universal SIE to be a cost-effective. If health state utilities derived from a population younger than 12 years were applied throughout the model, the universal SIE strategy cost \$844,628,820 per QALY during the model. When differential health state utilities were used for individuals younger than 12 years and 12 years and older, the universal SIE strategy cost \$687,358,873 per QALY in the cohort analysis. Similarly, universal SIE was not cost-effective at older AIT ages (cohort incremental cost-effectiveness ratio at start age of 25 years: \$749,723,253; 40 years: \$878,394,764; 60 years: \$1,286,810,154). Inclusion of indirect costs did not significantly change the results of the analysis (\$669,327,800 per QALY in the cohort and dominated in the microsimulation). Additional deterministic (Fig. 3) and probability sensitivity analyses (Fig. 4) did not demonstrate any iteration in which a universal SIE approach was cost-effective.

Discussion

AIT is a safe and effective first-line treatment for AR, ARC, or stinging insect allergy and can be lifesaving in the case of allergy. Although infrequent, SRITs are a significant concern for patients and practitioners but are very rarely fatal (although fatalities occur annually but at a rate significantly lower than death from lightning strike, in comparison).²⁹ SRITs are tracked closely at a national level with practitioner-initiated voluntary reporting through the AAAAI and ACAAI, and these events are graded using internationally standardized criteria from the World Allergy Organization.

Our Markov model of aeroallergen AIT clearly show that universal prescription of epinephrine autoinjector (EAI) devices to all patients undergoing subcutaneous immunotherapy (SCIT) is not a cost-effective practice compared with a tailored, contextualized practice in which an EAI is only prescribed after a patient experiences an initial SRIT, even when high rates of SRITs are assumed. Essentially, the universal policy could be cost-effective in theory and only at grossly exaggerated limits of sensitivity that would, in

Table 2
Cost-Effectiveness of Contextual vs Universal SIE for Allergen Immunotherapy

Strategy	Cost, \$	Incremental cost, \$	Effectiveness (QALY)	Incremental effectiveness	C/E, \$	ICER, \$/QALY	NMB, \$	Fatality	AIT early discontinuation	Total SR
Cohort										
Contextual SIE	16,955.21		25.56279654		663.28		2,539,324.45	–	–	–
Universal SIE	19,555.11	2599.90	25.56280043	0.00000388	764.98	669,327.730	2,536,724.94	–	–	–
Microsimulation, mean (SD) ^a										
Contextual SIE	16,232.14 (5204.32)		25.5786074551 (2.34537963)		634.60		2,541,628.61 (233,637.27)	0	0.4455 (0.4970)	0.1967 (0.4370)
Universal SIE	19,653.36 (4296.66)	3421.22	25.5555823395 (2.28525511)	–0.02302512	769.04	dominated	2,535,904.87 (227,463.93)	0	0.5485 (0.4976)	0.1795 (0.4194)

Abbreviations: AIT, allergy immunotherapy; C/E, cost-effectiveness; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALY, quality-adjusted life-year; SIE, self-injectable epinephrine; SR, systemic reaction.
^aThe microsimulation (n = 10,000) discontinued AIT in patients with more than 2 systemic reactions, and patients without SIE had a 25% reduction in patient-preference AIT discontinuation rates.

all practicality, never occur. These plausibly unrealistic conditions include a 25- to 30-fold reduction in current device acquisition costs, a nearly 1000-fold fatality risk reduction from using a device, and several hundred-fold increase in the rate of SRIT-related fatality. In the microsimulation, even despite the sensitivity levers, no iteration demonstrated cost-effectiveness of this policy given the limited annual incidence of SRIT-related fatality. Importantly, the microsimulation noted fewer early discontinuations with a contextual approach, which is a known issue for some patients receiving AIT who would rather discontinue therapy than carry an SIE and raises an important issue of values clarification and preference-sensitive care.

Most practices monitor monthly SRIT occurrence as a quality assurance measure and have strict rules regarding dose reductions and discontinuations after SRITs. Patients should be observed for 30 minutes after an AIT injection given that this is the timeframe in which an SRIT is most likely to occur. Although many allergists may universally prescribe SIEs to any patient in whom they initiate AIT, others wait until a patient has experienced an SRIT before prescribing SIE. The most recent AIT practice parameters do not offer clear guidance as to which strategy is recommended, and practice regarding this policy may vary considerably, as does the rate at which patients prescribed these devices actually use them after a systemic reaction.²⁰

Data from the most recent AAAAI/ACAAI SRIT surveillance study noted that SIE prescription rates were inconsistent, with only 24% to 30% of responding practices prescribing these all the time and up to 35% of practices reporting they prescribed these less than 10% of the time.²⁰ However, 29% of all practices responding to the last 2 years of the survey (2014–2016) reported prescribing EAls to more than 90% of their patients with AIT, mainly to prevent the delayed-onset SRIT occurring after the typical 30-minute observation time, although it was noted that few who were prescribed a device used it.²⁰ This survey concluded it was unclear whether prescribing SIEs for patients undergoing SCIT was a useful practice, which our analysis affirms. This may be a preference-sensitive care choice for which a decision aid could be useful.

This study has multiple limitations. First, the study is based on a simulation and construction of a theoretical model and plausible sensitivity ranges to test the model. Therefore, the model is subject to the validity of the assumption and inputs, and there could be multiple other ways to model this outcome. To ensure the robustness of the model, we used broad sensitivity ranges and sought to define even highly implausible assumptions to demonstrate any conceivable sensitivity under which the universal prescribing policy could work. Second, we compared 2 policies in which SIE was prescribed—either before an SRIT occurred or in response to an SRIT. This study did not explore a third strategy in which an EAI was not prescribed under any scenario, which could represent the most cost-effective option, but per data from the 2019 surveillance study is a limited practice at present. Third, this study focused only on the SIE preventing SRIT-related mortality as opposed to morbidity from serious but nonfatal reactions. Fourth, an interaction between recommended observation time and EAI prescription was not explored given the lack of data to inform this analysis. However, this interaction could be a key variable to help guide the necessity of EAI prescribing in patients receiving AIT and is an area for potential future study. Fifth, this analysis did not isolate risk for subgroups based on formulations of the AIT or additional patient comorbidities, although this variation was likely accounted for in the base aggregate data.

In conclusion, a practice of prescribing SIE to patients undergoing subcutaneous aeroallergen immunotherapy following an initial SRIT is more cost-effective than universally prescribing SIE to all patients. A universal prescribing strategy was only cost-effective under exceptionally exaggerated and unrealistic theoretical conditions of device

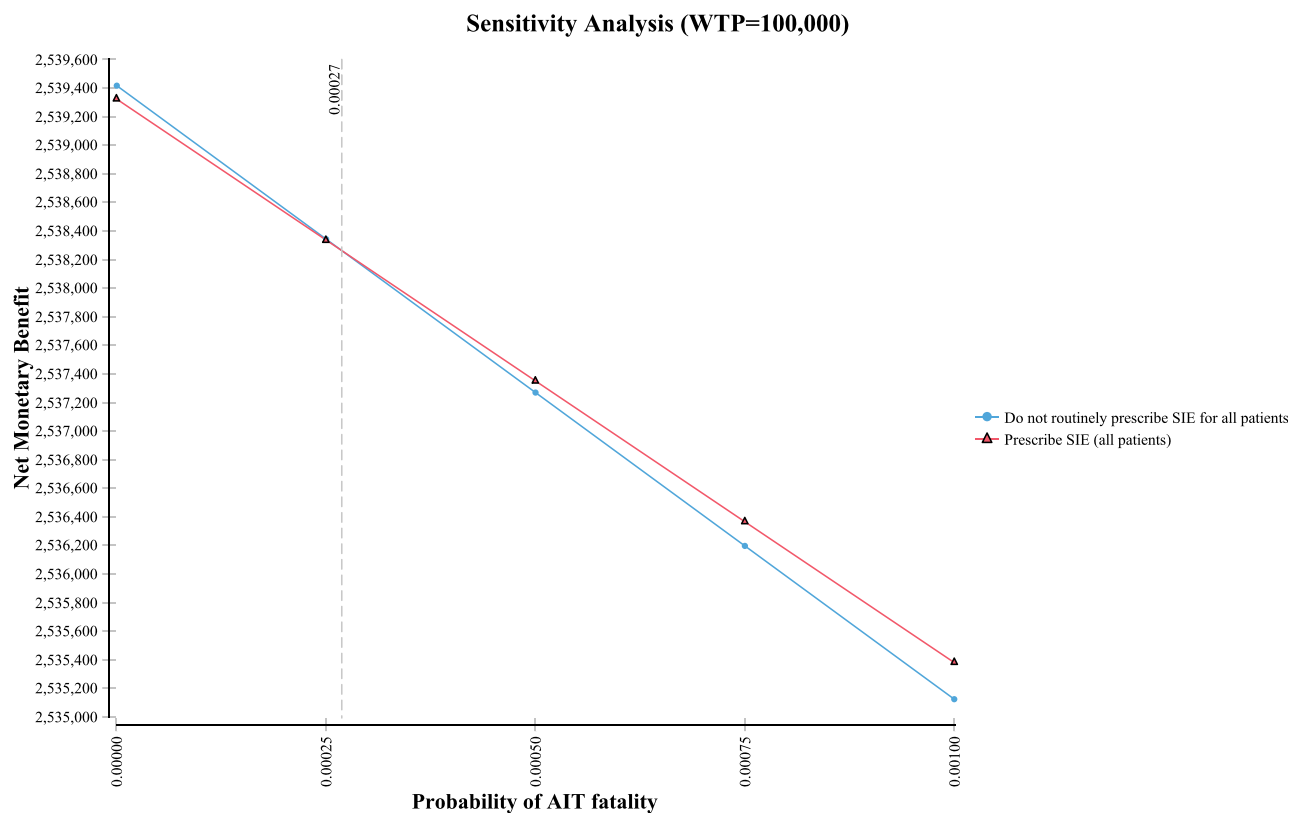


Figure 2. Deterministic sensitivity analyses. One-way sensitivity analysis of annual allergen immunotherapy (AIT) fatality and net monetary benefit (NMB) at a willingness to pay (WTP) of \$100,000 per quality-adjusted life-year, assuming annual self-injectable epinephrine (SIE) cost of \$24 and 1000 times fatality risk reduction from SIE.

Tornado Diagram – INMB, Routine SIE vs. Context Specific (WTP: 100,000)

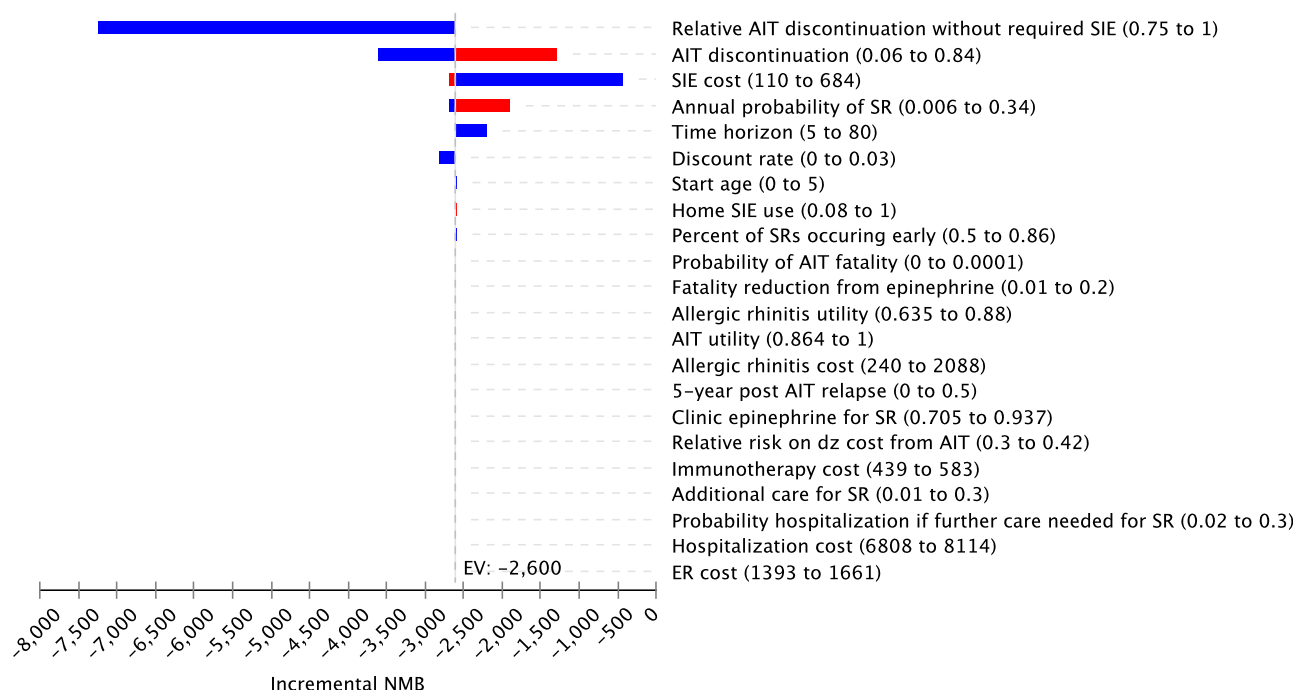


Figure 3. Tornado diagram. Sensitivity analyses across incremental net monetary benefit (NMB). Blue bars represent assumptions below the base case, and red bars represent those above the base case. Ranges with a negative incremental NMB are not cost-effective. AIT, aeroallergen immunotherapy; dz, disease; ED, emergency department; SIE, self-injectable epinephrine; SR, systemic reaction.

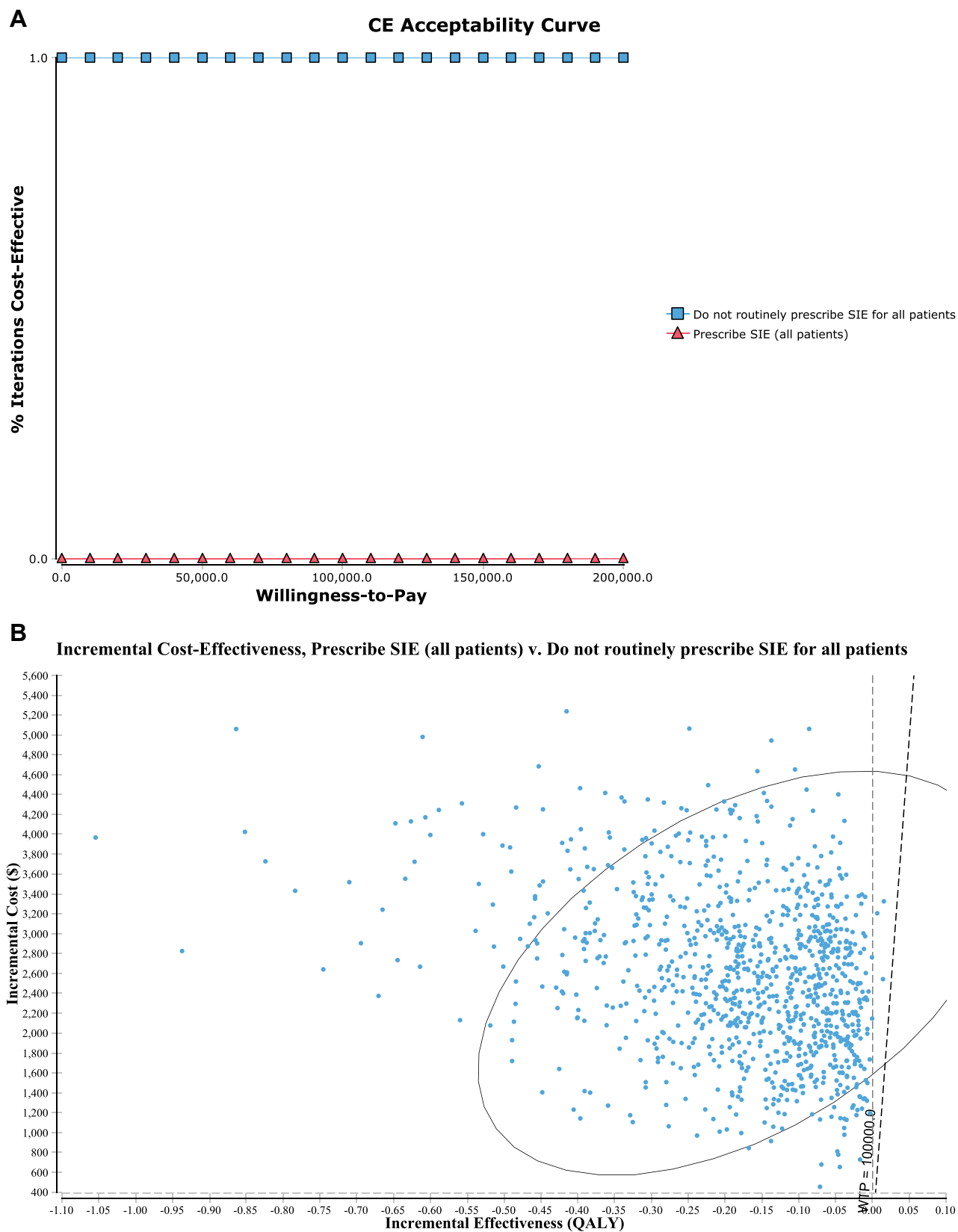


Figure 4. Probabilistic sensitivity analyses. In probabilistic sensitivity analyses, during an 80-year period ($n = 10,000$ simulations), universal self-injectable epinephrine (SIE) was not cost-effective in any simulation (willing to pay [WTP] = \$100,000 per quality-adjusted life-year [QALY]) when compared with a contextual approach. A, Cost-effectiveness (CE) acceptability curve. B, Incremental cost-effectiveness scatterplot.

cost, fatality risk reduction from device use, and likelihood of SRIT-related fatality. Although we cannot exclude that certain subgroups may differentially benefit from the universal policy based on particular preexisting risk or that this may represent a highly preference-sensitive care choice, this represents a potentially low-value practice when intended to prevent the outcome of a fatal SRIT, which is an exceedingly rare event occurrence. We hope that this analysis can help better inform a practice style where a notable knowledge gap exists.

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