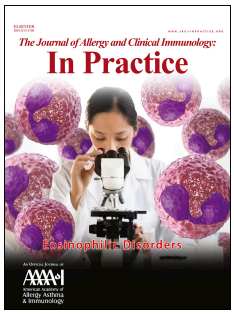

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Estimation of Health and Economic Benefits of Clinic Versus Home Administration of Omalizumab and Mepolizumab

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Abbreviations: ED (emergency department); WTP (willingness to pay); CEA (cost-effectiveness analysis);

Conflicts of Interest

Marcus Shaker: has a family member who is CEO of Altrix Medical and is a member of the Joint Taskforce on Allergy Practice Parameters.

Aaron Briggs: None

Ahmad Dbouk: None

Emily Dutille: None

John Oppenheimer:
Research/Adjudication: AZ, GSK, Sanofi, Novartis
Consultant: GSK, AZ, Sanofi
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Matthew Greenhawt: is supported by grant #5K08HS024599-02 from the Agency for Healthcare Quality and Research; is an expert panel and coordinating committee member of the NIAID-sponsored Guidelines for Peanut Allergy Prevention; has served as a consultant for the Canadian Transportation Agency, Thermo Fisher, Intrommune, and Aimmune Therapeutics; is a member of physician/medical advisory boards for Aimmune Therapeutics, DBV Technologies, Nutricia, Kaleo Pharmaceutical, Nestle, and Monsanto; is a member of the scientific advisory council for the National Peanut Board; has received honorarium for lectures from Thermo Fisher, Before Brands, multiple state allergy societies, the ACAAI, the EAACI; is an associate editor for the Annals of Allergy, Asthma, and Immunology; and is a member of the Joint Taskforce on Allergy Practice Parameters.

ABSTRACT

Background: Biologic therapy is a paradigm-shifting management strategy for many patients with asthma and chronic urticaria, but concerns for therapy-associated anaphylaxis may limit access to these therapies for patients unable to travel to medical clinics.

Objective: To characterize the cost-effectiveness of in-clinic vs. at-home biologic therapy with omalizumab and mepolizumab.

Methods: Economic evaluation using microsimulations was performed from societal and healthcare sector perspectives for patients with asthma or chronic spontaneous urticaria receiving omalizumab or mepolizumab in an Allergy clinic, primary care provider (PCP) office, or at home over a 1-year time horizon (12 injections per year in each base-case with sensitivity analysis to 24 injections per year). Travel times and distances were applied to a population attending a tertiary-care allergy clinic in Northern New England receiving omalizumab or mepolizumab, using a Willingness to Pay (WTP) of $10 million per death-prevented and in-clinic administration reducing anaphylaxis fatality and hospitalization 10-to-100-fold. Deterministic and probabilistic sensitivity analyses were performed.

Results: One-way Allergy clinic travel distances significantly exceeded local PCP offices (49 miles, 95% CI 42-56, vs. 12 miles, 95% CI 10-15). In the omalizumab societal analysis, annual PCP and Allergy clinic administration cost $1,369.14 (SD, $51.33) and $1,916.68 (SD, $40.86), respectively. Small reductions in medication-related fatalities with in-clinic administration were offset by the potential increase in automobile fatalities resulting from traveling to the Allergy

clinic (14.6 per million person-years for this strategy, SD 15.0). Compared to at-home administration, in-clinic omalizumab administration was not cost-effective, with an incremental cost-effectiveness ratio (ICER) of $500,648,430 (PCP), and with Allergy clinic administration dominated by higher costs and automobile-related fatalities. Routine mepolizumab clinic administration was dominated by at-home administration unless anaphylaxis rates or self-administration teaching costs were high.

Conclusions: For many patients, at-home administration of omalizumab or mepolizumab may be a cost-effective strategy.

HIGHLIGHTS

What is already known about this topic? Biologic therapy for asthma and urticaria is safe and effective for most patients, but anaphylaxis risk has historically limited access to at-home administration.

What does this article add to our knowledge? For most patients, at-home administration of omalizumab and mepolizumab is a cost-effective option. The in-clinic mitigation of therapy-related anaphylaxis risk is offset by increased risk of automobile-related fatality.

How does this study impact current guidelines? Home administration may be an appropriate consideration for many patients receiving omalizumab or mepolizumab. This is associated with lower overall risk to the patient, lower costs, and increases access to these therapies.

INTRODUCTION

In 2007, the Omalizumab Joint Task Force established a series of recommendations based on a review of Genentech omalizumab clinical trial and post-approval surveillance data, which advised the administration of omalizumab to be limited to physicians working in clinical settings.[1] This recommendation was established in response to the 0.09% risk of anaphylactic reactions following administration of omalizumab noted in clinical trial data, as well as the black box warning being placed on the package.[2] Subsequently, continued observation of post-marketing reports suggested the estimated frequency of omalizumab-related anaphylaxis was at least 0.2%, and the product insert language has been updated.[2] While in-clinic administration of omalizumab may allow for observation for development of anaphylaxis and improved reaction management, the opportunity cost and travel-related risks associated with administration of omalizumab and similar biologics in a clinical setting has not been defined (Table 1).[2-7] However, delayed anaphylaxis may occur despite in-clinic observation.[8,9] Recently, the European Commission approved omalizumab self-administration across all indications,[10] a practice facilitated with the availability of omalizumab pre-filled syringes.[11] European guidance suggests that omalizumab may be administered by trained lay-caregivers from the fourth dose onward, if deemed appropriate by the treating physician.[10] Similarly, the recent approval of mepolizumab for home administration illustrates an evolving paradigm of risk management and healthcare delivery (with other biologics following suit).[3,12]

The approach of mandated clinic observation instituted for some biologics may require patients to frequently travel long distances to specialty clinics, often with limited or absent evening and weekend access. Given that evidence suggests lay-caregivers are able to

successfully perform home administration,[13] the cost-effectiveness of clinic biologic administration is an important unanswered question. We therefore undertook this cost-effectiveness analysis of clinic-observed biologic administration to clarify the health and economic benefits of this practice.

METHODS:

Decision Model:

TreeAge Pro (Williamstown MA) was used to develop a decision model (Figure 1) to evaluate Monte Carlo microsimulations of hypothetical patients (n=100,000 per arm) receiving at-home vs. in-clinic administration of omalizumab or mepolizumab, with comparisons of both Allergy and Primary Care Provider (PCP) clinic administration of biologic therapies. Microsimulations were performed to estimate anaphylaxis and hospitalization rates. To isolate the effect of in-clinic vs at-home administration with respect to therapeutic costs and benefits of biologic therapies, a 1-year time horizon was used which assumed equivalent effectiveness between at-home and in-office administration. The threshold for cost-effective care was set at $10 million dollars per death prevented.[14] Because the effect of at-home administration on adherence is uncertain (home availability could increase or decrease adherence rates), this variable was not included in the base-case analysis; however, sensitivity analyses did include additional costs of home teaching and adherence monitoring. This analysis conformed to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guideline[15] and was approved by the Dartmouth College Committee for the Protection of Human Subjects.

Clinic Travel:

De-identified travel distances and travel times for the population of patients traveling to the Dartmouth-Hitchcock Medical Center (DHMC) Allergy Clinic for omalizumab and mepolizumab were collected from September 1, 2016 to October 7, 2018. For each patient identified the city and state of residence was used to record travel time and distance using Google Maps. Travel time and mileage to the Allergy clinic and the patient's PCP of record were recorded.

Costs:

Table 2 details model assumptions. Direct costs of in-clinic administration were estimated from healthcare claims data compiled and maintained by FAIR Health, Inc. after permissions for data use were obtained (the authors are solely responsible for research and conclusions reflected in this article and FAIR Health is not responsible for the conduct of the research or for the opinions expressed in this article).[16] Costs of in-clinic injections (code 96372) included the primary medical procedure and hospital outpatient facility fee. Total in-network costs of medication administration were used in the base-case model. Average automobile fuel price and economy were incorporated into the model,[17,18] in addition to average hourly wage to reflect indirect costs associated with clinic biologic administration.[19] All patients experiencing anaphylaxis assumed costs of emergency department (ED) evaluation, and those with severe anaphylaxis assumed additional costs of hospitalization. Patients receiving injections at home and at primary care sites also experienced costs of emergency transport to the ED; however, as the DHMC Allergy clinic (Lebanon, NH) is attached to an ED, medical center transportation costs were excluded from the Allergy clinic (which we presume to be

the case for most academic allergy practices similar to the one modeled in this analysis). The costs of ED visits and hospitalizations were derived from Clark et al. who reported data from 11,972 individuals with an ED visit or hospitalization from January 1, 2002 to December 31, 2008.[20] All costs were expressed in January 2019 dollars,[19] with a mid-point conversion date of January 1, 2005 used for Clark et al.[19,20]

Probabilities:

Published literature was incorporated to represent risks of anaphylaxis, hospitalizations, and fatalities, with *a priori* risk reductions assumed for in-clinic administration ranging from 10-fold to 100-fold. The rate of occurrence of anaphylaxis related to omalizumab and mepolizumab administration was modeled at 0.2% and 0.1% per patient, respectively.[2,3] Case-anaphylaxis fatality was estimated at 0.33%, based on a population-based epidemiologic study of three national databases reported by Ma et al.[21] The rate of severe anaphylaxis necessitating hospitalization was based on Clark et al. who reported 22% of patients seen with anaphylaxis required hospitalization.[20] As the incremental health-state utility between in-clinic vs at-home biologic administration is unknown, quality-adjusted life-years (QALY) were not used as an outcome measure and instead the analysis evaluated cost per fatality prevented.

Sensitivity Analyses:

Base-case analyses were performed from the societal perspective with additional sensitivity analyses including the healthcare sector perspective (excluding fuel and job-related indirect costs). Additional sensitivity analyses were performed with home teaching/adherence

monitoring costs modeled at $1,500. Medication and in-clinic observation was estimated at 40 minutes in the base-case with sensitivity ranges modeled to 130 minutes. In the base case 12 injections of each medication were assumed, with 24 injections of omalizumab evaluated in sensitivity analyses. In-clinic administration-related protection against anaphylaxis hospitalization and fatality was 10-fold in the base-case with 100-fold protection modeled in sensitivity analyses. Further analyses were performed across variable ranges by deterministic and probabilistic sensitivity analyses with modal triangular distributions. Triangular distributions were used to incorporate base assumptions as modal distributions with extreme value probabilities minimized, and were validated using alternative beta distributions for probabilities and fatalities with gamma distributions for costs and times.

RESULTS

Travel Times and Distances:

For both omalizumab and mepolizumab, travel times and distances to the Allergy clinic exceed those to the PCP office by significant margins. For omalizumab, one-way Allergy travel distance was 49 miles (95% CI, 42-56 miles) compared with a distance to the PCP of 12 miles (95% CI, 10-15 miles), translating to one-way travel time of 59 minutes (95% CI, 51-66) for Allergy clinic vs. 19 minutes (95% CI, 16-22) for the PCP office. Similar findings were observed for patients receiving mepolizumab (Allergy: 39 miles, 95% CI 29-49 miles; 46 minutes, 95% CI 37-56 minutes; PCP: 14 miles, 95% CI, 10-17 miles; 21 minutes, 95% CI, 16-25 minutes).

Cost-Effectiveness:

In the omalizumab analysis, the costs of either type of observed injection strategy were greater than the home injection strategy: Allergy clinic $1,916.68 (SD, $40.86), PCP administration $1,369.14 (SD, $51.33), and home injection $7.47 (SD, $213.66). Small reductions in medication-related fatalities were noted with in-clinic administration (home: 6.8 fatalities per million person-years, SD 149.6; PCP: 4.1 fatalities per million person-years, SD 15.0) but these were offset by increased automobile fatalities attributable to having to travel longer distances to the Allergy clinic (14.6 fatalities per million person-years in this strategy, SD 15.0). In-clinic administration of omalizumab was not cost-effective, with an incremental cost-effectiveness ratio (ICER) of $500,648,430 at a PCP office. Administration in the Allergy clinic was dominated (e.g, of all options compared, this resulted in the worst comparative health outcomes and highest cost) with both higher costs and fatalities attributable to automobile travel (Table 3). Modeling an extreme scenario in a sensitivity analysis where in-clinic (either venue) administration was associated with a 100-fold reduction in the risk of anaphylaxis hospitalization and fatality risk still remained cost-ineffective, with PCP and allergy clinic ICERs above $10 million per death prevented (PCP: $463,456,793; Allergy: dominated). When evaluating fatality risk, patients living more than 24 miles from the clinic were at a higher risk of automobile fatality than anaphylaxis fatality.

Clinic administration of mepolizumab resulted in greater fatalities (from anaphylaxis and automobile accidents combined) whether patients travelled to PCP or Allergy offices (per-strategy deaths per million persons at home: 3.1, SD 102.2; PCP office: 4.3, SD 10.2; Allergy clinic: 11.4, SD 10.2). From a societal perspective, administration-related costs were greater in both the PCP and Allergy clinic (home: $4.40, SD $166.59; PCP office: $1,396.35, SD

247 $454.88; Allergy clinic: $1,744.00, SD $40.86). Clinic administration remained dominated
248 in the PCP and Allergy clinic models even assuming a 100-fold risk reduction for
249 anaphylaxis hospitalization and fatality.
250
251 *Sensitivity Analyses*
252 Additional microsimulation with 1 million subjects randomized to each strategy did not
253 change overall results. Additional Monte Carlo simulation with alternate random number
254 seeding demonstrated similar findings, with a PCP vs home administration ICER of
255 $641,000,659. Multiple additional analyses were performed to determine critical levers
256 where these practices could potentially attain cost-effectiveness. Increasing the degree of in-
257 clinic protection to a 1,000-fold fatality risk reduction still did not result in cost-effective care
258 (omalizumab ICER $426,098,636 for PCP vs home administration, Allergy clinic
259 administration dominated). Excluding wage costs, in-clinic administration remained cost-
260 ineffective (omalizumab PCP vs home administration $364,952,038 with Allergy-clinic
261 administration dominated).
262
263 Omalizumab PCP-clinic administration became cost-effective as rates of anaphylaxis
264 increased above 4.2%, anaphylaxis case-fatality rate exceeded 7.7%, or if additional teaching
265 and adherence costs reached $1,336.29 (Figure 2), with an interaction seen between risk of
266 anaphylaxis and case-fatality rate (Figure 3). Given longer travel distances to Allergy clinic,
267 this strategy was not cost-effective unless risks for omalizumab anaphylaxis reached 6.2%,
268 case-fatality exceeded 11.3%, or teaching costs reached $1,988.66. Probabilistic Sensitivity
269 Analysis (n=10,000 simulations) demonstrated home administration to be the most cost-

effective strategy of the 3 options in 91.7% of omalizumab simulations (Figure 4). Similar to the omalizumab analysis, PCP administration of mepolizumab could be cost-effective if the rate of mepolizumab anaphylaxis exceeded 4.4%, case-anaphylaxis fatality rate of 15.9%, or teaching/adherence costs reached $1,402.51. Probabilistic Sensitivity Analysis (n=10,000 simulations) demonstrated home administration to be the most cost-effective strategy in 92.7% of mepolizumab simulations (Figure 4). Using alternative distributions without adherence costs, home administrations was the most cost-effective option in 99.9% of omalizumab simulations and 99.7% of mepolizumab simulations

Evaluation of clinic-administered omalizumab from the healthcare sector perspective resulted in PCP and Allergy strategy costs of $901.66 (SD, $75.96) and $900.6 (SD $66.72), respectively, for a PCP vs home strategy ICER of $445,861,774. The Allergy clinic strategy remained dominated by the home strategy, and mepolizumab was similarly dominated by home administration from this perspective.

DISCUSSION

While recent changes in European practice have created an avenue for home administration of omalizumab, in the United States, current recommendations advocate for administration of omalizumab in a medical clinic. This is due in equal parts to previous lack of availability of a pre-filled omalizumab syringe and the fact that this had to be reconstituted, as well as the aforementioned risk of anaphylaxis and black box warning from the FDA accompanying the drug. Allergy and pulmonary clinics serve as the most common setting of omalizumab administration; however, in many parts of the country access to subspecialty care requires

significant travel burdens compared to local primary care settings. Our study highlights this reality at a tertiary care medical center in Northern New England, where patients receiving omalizumab travel significantly longer distances to receive omalizumab administration in Allergy clinic relative to more proximal PCP offices (with an average additional distance traveled of 37 miles). Given the longer travel distances, patients experience significant risks of traffic accidents and fatalities, important variables that we may not readily consider when weighing recommendations for in-office administration of products to protect against small risks. Travel distances may vary by location, with greater or lesser disparities between Allergist and PCP travel distances noted contextually. However, despite current practice standards being what they are, on the balance, requiring in-clinic omalizumab administration in the United States does not appear cost-effective, specifically with Allergy clinic administration potentially leading to both greater costs and overall fatalities in the simulation reported here. While administration at PCP offices is unusual (which we recognize is not a realistic option in many circumstances and was only included for cost comparison), even in this setting mandated clinic-observed omalizumab administration is not cost-effective, with the ICER exceeding $500 million dollars per death prevented from a societal perspective.

Our analysis suggests patient-specific scenarios may exist to justify clinic-observed omalizumab administration. For example, if significant teaching costs or adherence concerns exist, or if risk of anaphylaxis or case-fatality is high clinic observation would be appropriate. However, in more rural setting such as ours, extended travel to subspecialty clinics to receive biologic therapy does not seem justified in most circumstances. While preference data do not exist exploring this area as of yet, it is also presumable that this could represent a preference-sensitive care area for

patients who value the in-office pathway, where shared decision-making and use of a decision-aid could also play a role. We could not model this as of yet, however.

Strengths of our analysis include incorporation of home education and adherence monitoring costs, because a legitimate concern of home biologic administration may be that adherence may fall without health care provider supervision. However, whether or not adherence would actually increase or decrease is unknown, because improved access to therapy for patients who no longer need to travel hours for therapy may actually offset a decrease in home adherence. The incorporation of home adherence devices for biologic administration will be valuable to ensure home administration as prescribed. Such adherence monitors can effectively interact with medical devices and relay real-time information to providers and pharmacies through cloud computing.[22] The issue of ensuring adherence to home biologic therapy cannot be overstated, and in the end may be the most critical piece of the puzzle in improving asthma management.[23]

Our analysis does have limitations. First, as a simulation it is dependent on strength of inputs used, and is an approximation of how "real life" may unfold, and as such this should be kept in perspective. Second, this is a novel concept that has exceptionally limited prior literature to help guide plausible assumptions. Third, our travel time and distances were derived from the clinic population of a rural tertiary care medical center in Northern New England, so it is quite possible that our travel times to allergy clinic may be less applicable to travel distances in a more urban setting, or in states with higher densities of other academic medical centers and we did not evaluate differential costs for pediatric vs adult patients. However, one-way travel distances and times of 12 miles (19 minutes) to a PCP office may be more reflective of national median values.

Although, as noted earlier, significant variation in travel distance may occur based on geographic location. Sensitivity analyses were performed to address this limitation, with one-way travel distances and times of 6 miles (9.5 minutes) to a PCP office modeled. Fourth, we intentionally did not model health state transitions, extended model horizons, costs associated with access barriers to biologics, lost opportunities to improve disease control and their consequences in healthcare utilization. While incorporating these aspects of care into more complex models could provide additional perspective on cost-effectiveness, the intent of this analysis was to specifically evaluate the practice of observed biologic administration. There may be a role for further investigation of models with longer time horizon, all-cause age-adjusted mortality, and health state transitions, but unless a large differential effect occurs with therapy adherence these factors would not be expected to impact the model conclusions. Fifth, we excluded ED transport costs for Allergy clinic anaphylaxis; however, the addition of these costs would only make this strategy less-cost-effective. Sixth, we did not specifically model the practice of home biologic administration in patients with prior episodes of anaphylaxis, and excluded patients with known hypersensitivity to omalizumab and mepolizumab from the respective analyses. Similar to patients with very poorly controlled asthma despite biologic therapy, a history of biologic anaphylaxis could increase risk for more severe anaphylaxis where home administration would be less desirable. Seventh, we did not evaluate differential cost of epinephrine autoinjectors (as it was assumed there was no differential self-injectable epinephrine preparedness between groups and because all patients would have one irrespective of where the biologic was administered) or patient-preference sensitive shared decision-making regarding emergency medical care in the setting of resolved anaphylaxis at home. The potential delayed nature of anaphylaxis with omalizumab creates an indication for self-injectable epinephrine (SIE) for all patients, which

means that SIE cost will be the same, because being monitored in the office does not remove all risk.[9] Eighth, shared decision-making should also have a role in the setting of biologic administration, and there may be a role for the development of formal decision aids to assist in this process which could influence cost models. Ninth, it is important to note that home administration could shift coverage of biologic therapy by some insurers with difference in costs that could impact patients; however, from a societal perspective these changes would not be expected to impact model conclusions. Tenth and lastly, additional medication procurement costs, more extended lost-productivity costs and time-away from school for clinic travel was not modeled, which could make in-clinic administration even more costly. However, the model did account for potential under-employment due to severe asthma with an analysis excluding wage-costs. Medication procurement was not included in the model due to unknown variation between clinic and home administration in terms of in home-delivery, pharmacy travel distance, and frequency of medication pick-up.

In summary, routine administration of clinic-observed omalizumab or mepolizumab does not appear to be cost-effective practice in most situations. The current analysis supports the recent label change for mepolizumab home administration, and suggests that the United States should explore the risks and benefits of adopting an approach similar to the Europe for omalizumab administration with the advent of pre-filled omalizumab syringes. While we as a field focus on patient safety related to medications in the office, and above all else are cautious to protect against the risk of anaphylaxis, there should be consideration for the trade-offs we unintentionally ask our patients to assume in the risk related to automobile travel to the office, which may be the greatest risk a patient assumes that particular day.

386

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Figures and Legends:

Figure 1: Evaluation of Health and Economic Benefits of Clinic Vs. Home Biologic Administration

Figure 2: Deterministic cost-effectiveness analysis are shown for omalizumab (panel a) and mepolizumab (panel b) with red bars indicating values above and blue bars those below the base-case analysis. Tornado diagrams of Incremental Net Monetary Benefit (INMB) are shown with PCP clinic strategy compared with Home administration strategy, with prevented fatalities converted to dollars at a Willingness to Pay (WTP) at $10,000,000 per death prevented. Positive values are considered cost-effective. Expected Value (EV) shows the base-case analysis.

Figure 3: Sensitivity Analyses of omalizumab anaphylaxis risk vs anaphylaxis fatality risk. Colors denote cost-effective care at a Willingness-To-Pay (WTP) of $10,000,000 per death prevented.

Figure 4: Probabilistic Sensitivity Analysis using modal triangular distributions for omalizumab (a) and mepolizumab (b) from a societal perspective demonstrated home administration to be most cost-effective in 91.7% of omalizumab and 92.7% of mepolizumab simulations (n=10,000 each) at a WTP of $10,000,000 per death prevented.

Table 1: Incidence of Anaphylaxis with Selected Biologics

Biologic	Manufacturer	Mechanism of action	Incidence of anaphylaxis	In-clinic administration recommended on product labeling?
Dupixent *(dupilumab)*	Sanofi Genzyme	Inhibits IL-4 and IL-13	Not reported	No
Enbrel *(etanercept)*	Amgen	TNFα inhibitor	<2%	No
Fasenra *(benralizumab)*	AstraZeneca	IL-5 antagonist	Not reported	Yes
Humira *(adalimumab)*	Abbvie	TNFα inhibitor	Approximately 1%	No
Nucala *(mepolizumab)*	GSK	IL-5 antagonist	Not reported	Optional
Xolair *(omalizumab)*	Genentech	Anti-IgE	≤ 0.2%	Yes

Table 2: Model Inputs and Assumptions

Input	Value	Range	Reference
Cost of clinic injection, code 96372	Primary Medical Procedure: In-Network Price: $42; Out-of-Network Price: $90; Hospital Outpatient Facility fee: In-Network: $33; Out-Of-Network: $94; Total Costs: In-Network: $75; Out-of-Network: $184 Base Assumption: $75	$75 - $320	FairHealthConsumer.www.fairhealthconsumer.org Accessed June 15, 2019
Automobile fatality rate	1.18 per 100 million vehicle miles travelled	0.118 - 1.18 per 100 million vehicle miles travelled	Traffic Safety Facts 2016 Data. www.crashstats.nhtsa.dot.gov Accessed June 15,2019.
Automobile fuel price and economy	$2.68 per gallon, regular 23 miles per gallon	$ 1.98 - $3.50 per gallon (18 - 39 mpg)	Irving.www.theirving.com. Accessed June 15, 2019; Best and Worst Gas Mileage 2018. www.cars.com. Accessed June 15, 2019
Omalizumab Clinic Travel (one-way)	Allergy miles: 49 (95% CI, 42-56); Allergy travel: 59 minutes (95% CI, 51-66); PCP miles: 12 (95% CI, 10-15); PCP travel: 19 minutes (95% CI, 16-22); Number of visits per year: 12-24	Allergy clinic: 24.5 - 98 miles (30 - 120 minutes); PCP: 6-19.5 miles (9.5 - 38 minutes);	Practice Survey DHMC, n = 134
Mepolizumab Clinic Travel (one-way)	Allergy miles: 39 (95% CI, 29-49); Allergy time: 46 minutes (95% CI, 37-56); PCP miles: 14 (95% CI, 10-17); PCP time: 21 minutes (95% CI, 16-25); Number of visits per year: 12	Allergy clinic: 19.5 - 78 miles (23 -92 minutes); PCP: 7 - 19.5 miles (10.5 - 42 minutes)	Practice Survey DHMC, n = 36
Average Hourly Wage	$27.83	$0 - $100	Bureau of Labor Statistics. www.bls.gov Accessed June 15, 2019
Omalizumab Anaphylaxis	0.2%	0.2% - 5%	Xolair [package insert]. South San Francisco, CA: Genentech, 2018
Mepolizumab Anaphylaxis	≤0.1%	0.1% - 5%	Nucala [package insert]. Research Triangle Park, NC: GSK; 2017; Personal communication.
Anaphylaxis Fatality	≤0.33%	0.33% - 1.3%	Ma L, Danoff TM, Borish L. Case fatality and population mortality associated with anaphylaxis in the United States. J Allergy Clin Immunol 2014; 133: 1075-83.
Annual Visits	12	12-24	model assumption
Clinic Wait Time	40 minutes	30 - 130 minutes	
Home Teaching	$0	$0 - $1,500	
Clinic Administration Fatality Risk Reduction	10x	10x - 100x	

Anaphylaxis Cost	Ambulance Transport: $470 (2007 USD); $585 (2019 USD); ED evaluation (all): $1,152 (2005 USD); $1,521 ($2019 USD); Hospitalization (22%): $5,652 (2005 USD); $7,460 (2019 USD)	Ambulance Trasnport: $400 - $1,500; ED evaluation: $900 - $2500; Hospitalization (5% - 50%): $2,500 - $2,000	Patel DA, Holdford DA, Edwards E, CArroll NV. Estimating the economic burden of food-induced allergic reactions and anaphylaxis in the United States. J Allergy Clin Immunol. 2011; 128: 110-115; Clark S, Wei W, Rudders SA, Camargo CA. Risk factors for severe anaphylaxis in patients receiving anaphylaxis treatment in US emergency departments and hospitals. Journal of Allergy and Clinical Immunology. 2014;134(5):1125-1130; CPI inflation Calculator. www.data.bls.gov. Accessed June 15, 2019

Note: Triangular distributions were evaluated using the modal value each variable bounded by the minimum and maximum ranges fitted to a triangle with maximum apical unit distribution at the mode and probability minimized at extreme values, and were validated by alternative beta distributions for probabilities and fatalities, and gamma distributions for costs and times.

Table 3: Cost-Effectiveness Analysis of Administration Strategies by Product

Strategy	Cost	Fatality (per million)	Net Monetary Benefit	Anaphylaxis	Hospitalization (per million)	ICER
Omalizumab						
Home Administration	$7.47 (SD, $213.66)	6.8 (SD, 149.6)	-$75.45 (SD, $1,666.28)	0.2% (SD, 4.5%)	420 (SD, 20490)	Dominant
PCP Clinic	$1,369.14 (SD, $51.33)	4.1 (SD, 15.0)	-$1,409.92 (SD, $185.56)		30 (SD, 5,480)	$500,648,430
Allergy Clinic	$1,916.68 (SD, $40.86)	14.6 (SD, 15.0)	-$2,062.25 (SD, $159.78)			Dominated
Mepolizmab						
Home Administration	$4.04 (SD, $166.59)	3.1 (SD, 102.2)	-$35.72 (SD, $1,156.85)	0.1% (SD, 3.1%)	270 (SD, 16,430)	Dominant
PCP Clinic	$1,396.35 (SD, $47.53)	4.3 (SD, 10.2)	-$1,439.16 (SD, $133.72)		30 (SD, 5,480)	Dominated
Allergy Clinic	$1,744.00 (SD, $40.86)	11.4 (SD, 10.2)	-$1,857.62 (SD, $116.57)			Dominated

QUESTION

Clinic vs Home Biologic Administration?

LOCATION

- **PCP office**
- **Allergy clinic**
- **Home**

INPUTS

Omalizumab or Mepolizumab

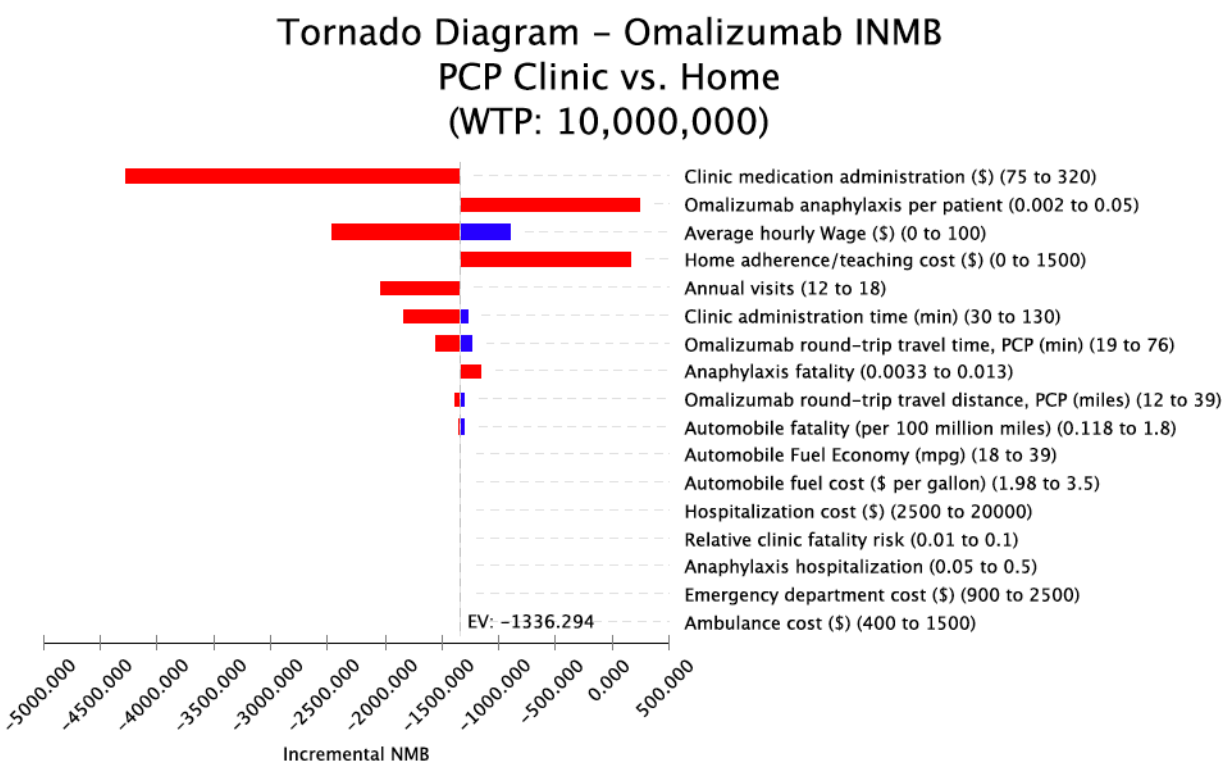
- **Cost of medication**
  - **Clinic injections**
  - **Home teaching and adherence monitoring (sensitivity analysis)**
- **Anaphylaxis**
  - **Medication specific anaphylaxis rates**
  - **Anaphylaxis case-fatality rates**
  - **Costs of ambulance transport, emergency care, hospitalization**
  - **10x (to 100x) fold risk reduction in anaphylaxis hospitalization and fatality rates for PCP or allergy clinic administration**
- **Travel costs (PCP and allergy clinics)**
  - **Automobile fatality risks**
  - **Job-related opportunity costs**
  - **Costs of travel to clinic**

OUTCOMES

- **Overall Costs**
- **Overall Fatalities**
- **Hospitalization Rates**
- **Cost per death prevented**

Figure 2

A.


Tornado Diagram – Omalizumab INMB
PCP Clinic vs. Home
(WTP: 10,000,000)
Clinic medication administration ($) (75 to 320)
Omalizumab anaphylaxis per patient (0.002 to 0.05)
Average hourly Wage ($) (0 to 100)
Home adherence/teaching cost ($) (0 to 1500)
Annual visits (12 to 18)
Clinic administration time (min) (30 to 130)
Omalizumab round-trip travel time, PCP (min) (19 to 76)
Anaphylaxis fatality (0.0033 to 0.013)
Omalizumab round-trip travel distance, PCP (miles) (12 to 39)
Automobile fatality (per 100 million miles) (0.118 to 1.8)
Automobile Fuel Economy (mpg) (18 to 39)
Automobile fuel cost ($ per gallon) (1.98 to 3.5)
Hospitalization cost ($) (2500 to 20000)
Relative clinic fatality risk (0.01 to 0.1)
Anaphylaxis hospitalization (0.05 to 0.5)
Emergency department cost ($) (900 to 2500)
Ambulance cost ($) (400 to 1500)
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-4500.000
-4000.000
-3500.000
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-2000.000
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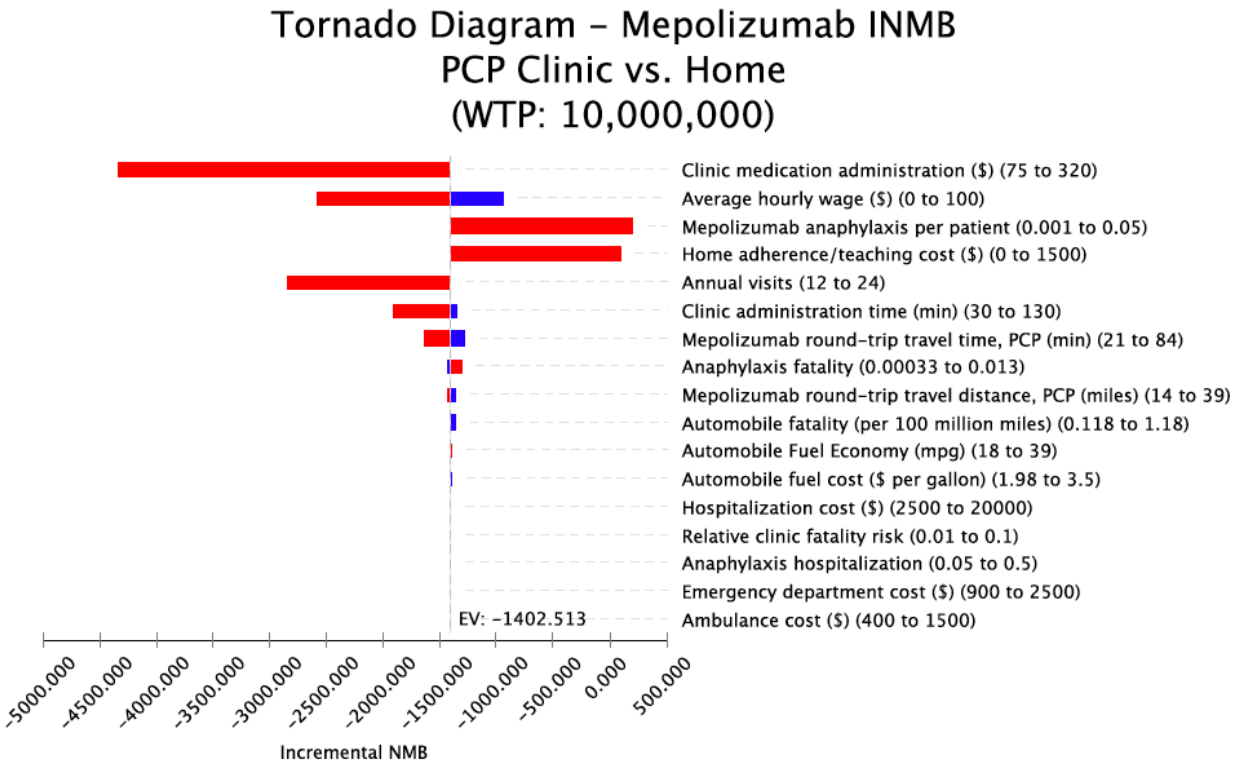
-1000.000
-500.000
0.000
500.000
Incremental NMB

B.


Tornado Diagram – Mepolizumab INMB
PCP Clinic vs. Home
(WTP: 10,000,000)
Clinic medication administration ($) (75 to 320)
Average hourly wage ($) (0 to 100)
Mepolizumab anaphylaxis per patient (0.001 to 0.05)
Home adherence/teaching cost ($) (0 to 1500)
Annual visits (12 to 24)
Clinic administration time (min) (30 to 130)
Mepolizumab round-trip travel time, PCP (min) (21 to 84)
Anaphylaxis fatality (0.00033 to 0.013)
Mepolizumab round-trip travel distance, PCP (miles) (14 to 39)
Automobile fatality (per 100 million miles) (0.118 to 1.18)
Automobile Fuel Economy (mpg) (18 to 39)
Automobile fuel cost ($ per gallon) (1.98 to 3.5)
Hospitalization cost ($) (2500 to 20000)
Relative clinic fatality risk (0.01 to 0.1)
Anaphylaxis hospitalization (0.05 to 0.5)
Emergency department cost ($) (900 to 2500)
Ambulance cost ($) (400 to 1500)
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-4000.000
-3500.000
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-2000.000
-1500.000
-1000.000
-500.000
0.000
500.000
Incremental NMB

Sensitivity Analysis

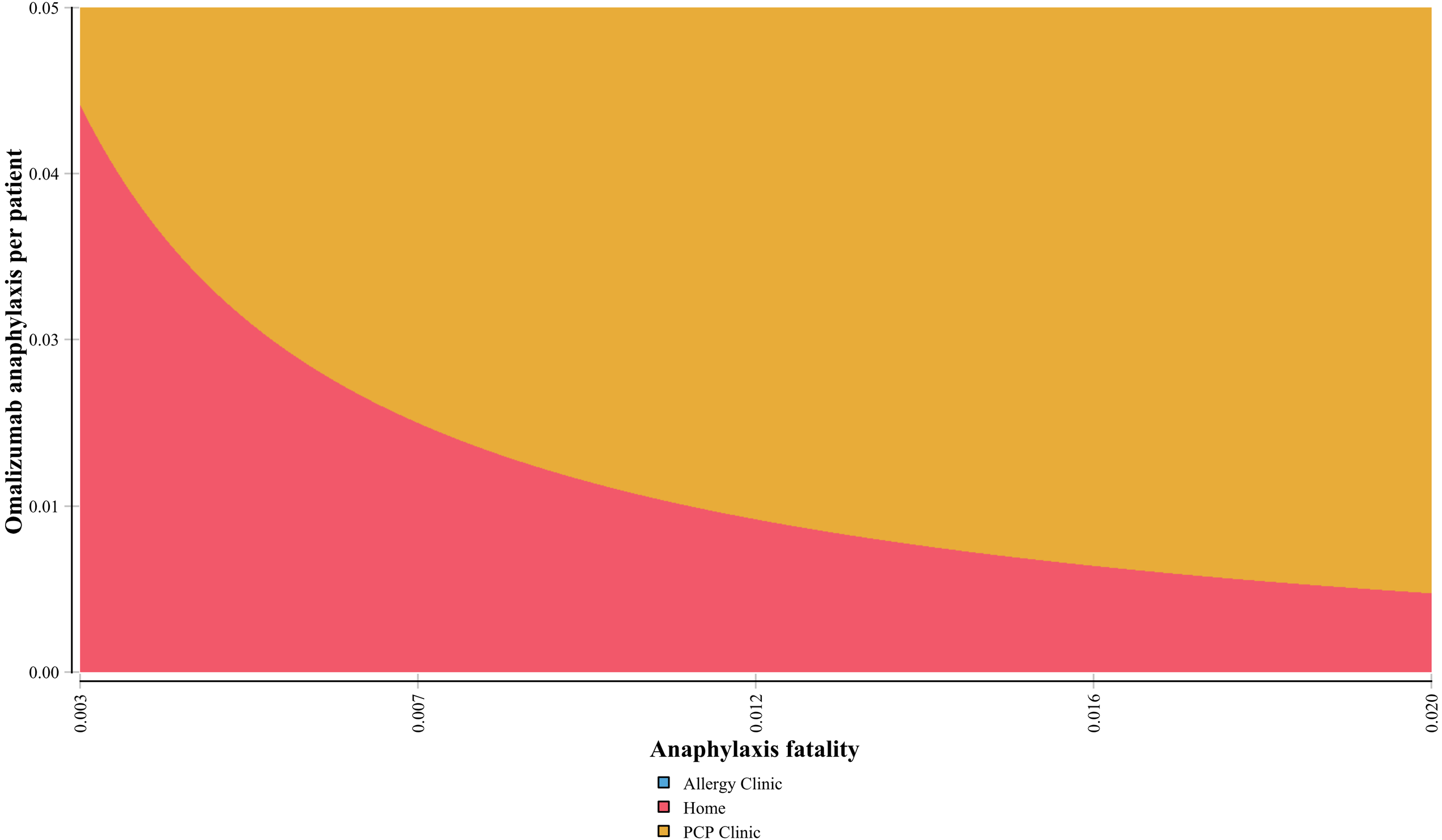
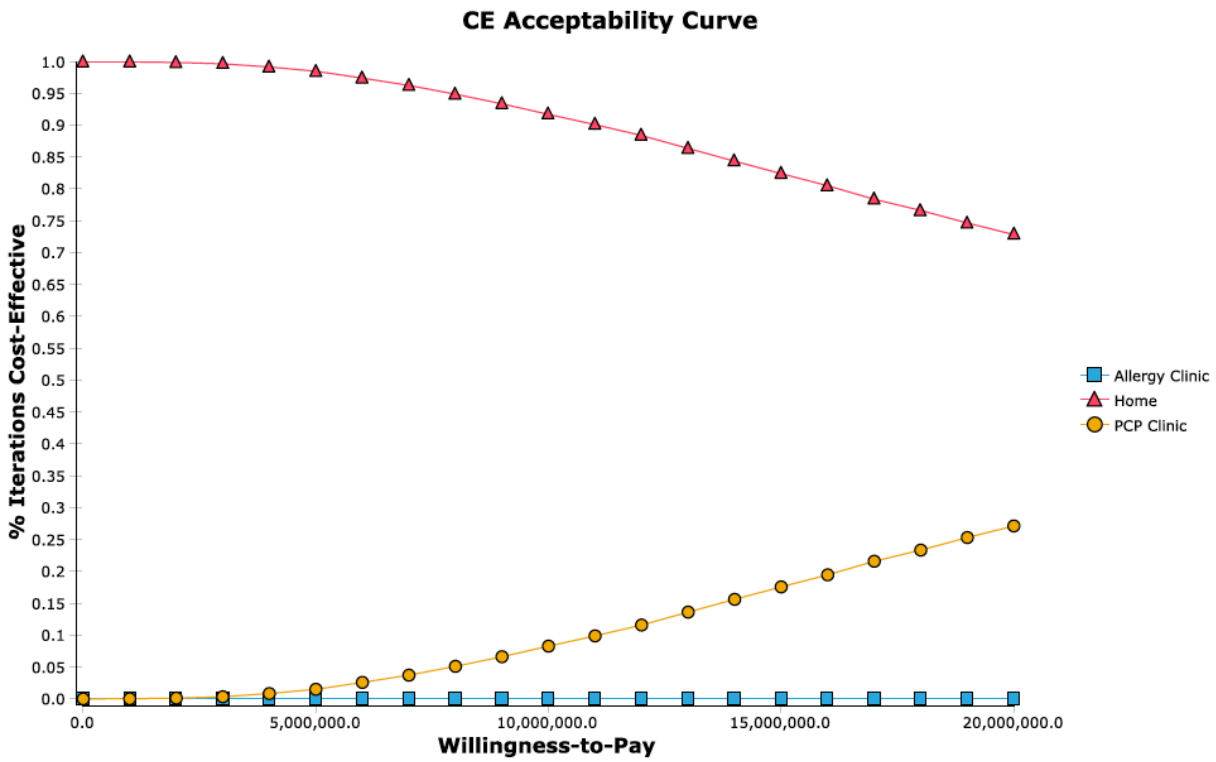


Figure 4

A.


CE Acceptability Curve
% Iterations Cost-Effective
Willingness-to-Pay
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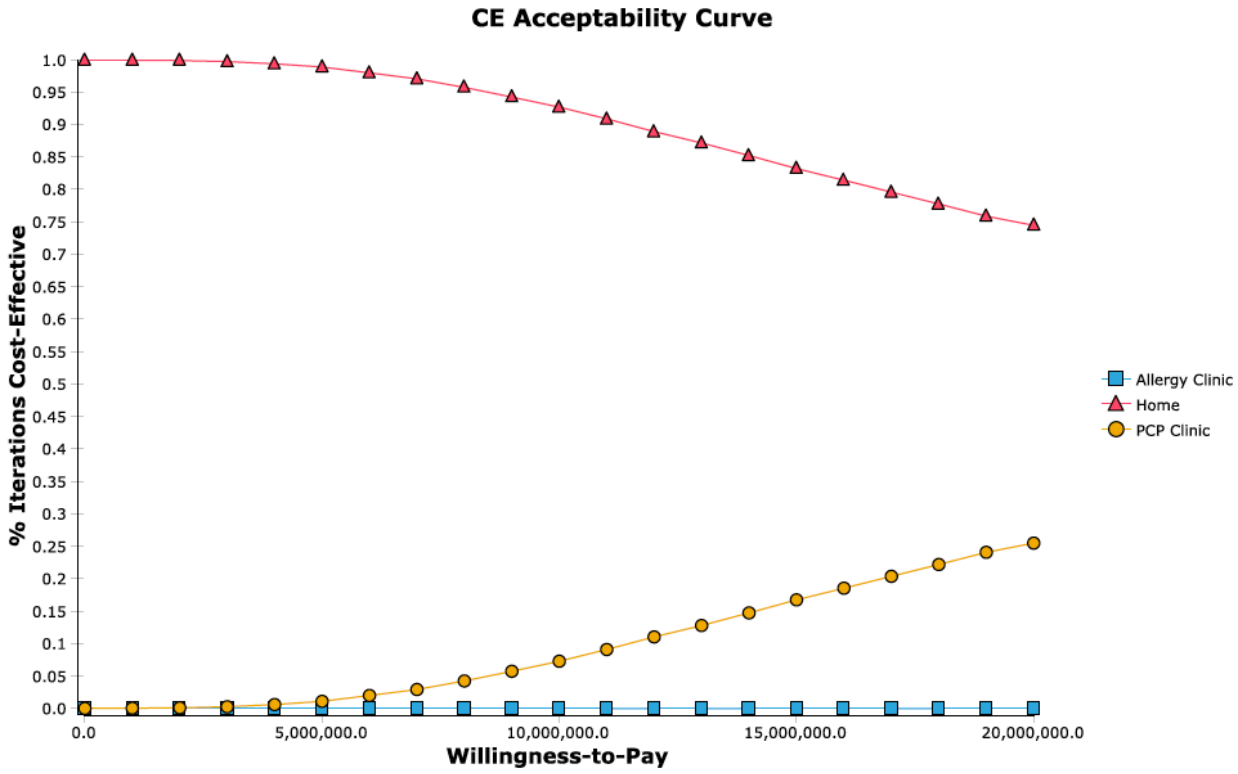
10,000,000.0
15,000,000.0
20,000,000.0
Allergy Clinic
Home
PCP Clinic

B.


CE Acceptability Curve
% Iterations Cost-Effective
Willingness-to-Pay
0.0
5,000,000.0
10,000,000.0
15,000,000.0
20,000,000.0
Allergy Clinic
Home
PCP Clinic