Performing Cost-Effectiveness Analyses to Support Policy Making: Key Lessons From the Assessment of Aducanumab

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Abstract

The purpose of this paper is to describe the process and the methods of cost-effectiveness analysis for clinicians interested in joining or leading aspects of this branch of evidence-based research. Cost-effectiveness is a useful tool for policymakers and is considered a starting point for discussions of fair pricing. Clinicians are important members of teams conducting cost-effectiveness analyses, particularly as it relates to integrating their clinical expertise into the decisions around the design and conduct of the analysis. Their input is essential in assuring that models adequately reflect clinical practice and are informed by expert judgments of how existing data can best be interpreted to build a comprehensive analysis of the clinical and economic outcomes of different treatment options. We illustrate specific contributions that clinicians are well positioned to make in these teams using a recent cost-effectiveness analysis of aducanumab that was conducted to support fair drug pricing. While discussing these contributions, we explain key components of a cost-effectiveness analysis, such as time horizon, health states, and perspective, to support the understanding of the methods of cost-effectiveness by the clinical researchers and to promote a common dialogue among these multidisciplinary teams.

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Introduction

A groundswell of US public support (recently polled at 88%) backs the idea of giving the federal government the ability to negotiate drug prices for Medicare.\(^1\) Whether or not Congress will enact the public’s wish, market failures unique to patent-protected drugs call for evidence-based tools to help inform judgments of what is a reasonable or “fair” price. This same need for having a framework to help determine fair pricing exists for public and private insurers, employers, and drug makers themselves.

The evidence-based framework that supports fair drug pricing is cost-effectiveness. Although assessments of the value of a drug or other intervention must always begin with an analysis of the comparative clinical effectiveness of the intervention, for this analysis to suggest specific fair price ranges, researchers must incorporate it within a broader analysis of cost-effectiveness. Therefore, as drug pricing has become a growing health policy concern, cost-effectiveness analysis has gained greater relevance as a method that can address some of the most important – and controversial – health system decisions in the US.

The purpose of this paper is to describe the process and the methods of cost-effectiveness analyses for clinicians interested in joining or leading aspects of this branch of evidence-based research. Clinicians are important members of teams conducting cost-effectiveness analyses, particularly as it relates to integrating their clinical expertise into the decisions around the design and conduct of the analysis. Their input is essential in assuring that models adequately reflect clinical practice and are informed by expert judgments of how existing data can best be interpreted to build a comprehensive analysis of the clinical and economic outcomes of different treatment options. Throughout this paper, we illustrate specific contributions that clinicians are well positioned to make in these teams using a recent
cost-effectiveness analysis of aducanumab as our thread throughout. We focus on three main areas in the construction of the cost-effectiveness model: 1) defining the scope of the analysis; 2) extrapolating beyond the available evidence; and 3) characterizing uncertainty. Within each focus area, we describe decisions on aducanumab modeling and how such decisions were supported with clinical expertise. We also briefly explain components of each focus area to support the understanding of the methods of cost-effectiveness by the clinical researchers and to promote a common dialogue among these multidisciplinary teams.

This narrative is not meant to be a standalone resource for those interested in learning all the steps involved with cost-effectiveness best practices. Rather, we explore the most consequential yet generalizable decisions our team made in designing the analysis of aducanumab and provide background information on key methodological areas within them. Throughout this narrative, we point to clinical experience as one guiding force in these decisions. In doing so, we hope clinical researchers and trainees will be better equipped to join and contribute to cost-effectiveness research teams. Of note, cost-effectiveness design decisions are grounded in measuring the treatment’s impact on patients, caregivers, and those who collectively pay. Therefore, well-informed design decisions are always centered around quantifying impacts of these key stakeholders.

**Contribution Area #1: Defining the Scope**

Clarifying the specific research objective(s) and the overall scope of the analysis is the first step in a cost-effectiveness analysis. In the scoping phase, one must first characterize the Population, Intervention, Comparator, Outcomes, and Time horizon (PICOT). Clinical researchers are already familiar with specifying the PICO. The unique addition necessary for a
cost-effectiveness is the time horizon, which is for how long the costs and consequences will be modeled. The time horizon should be as long as costs and consequences accrue. As an example, if a treatment is expected to influence survival, then a lifetime time horizon should be used to capture the potential lifetime survival gains. The aducanumab PICOT was identified through stakeholder engagement that included patients and patient advocates, clinicians, researchers, and manufacturers associated with this evaluation. The specified PICOT for the aducanumab evaluation formed the basis for the comparative-effectiveness evaluation and was expanded upon within the cost-effectiveness analyses.

The aducanumab Population may have required further discussion if the Food and Drug Administration (FDA) aducanumab label remained broader than the pivotal randomized controlled trial study populations, but this was resolved as of August 2021 to specify “in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials.” In discussion with clinical experts, the pairwise comparison featured in the two pivotal trials was consistent with the most appropriate Intervention and Comparator for both comparative effectiveness and cost-effectiveness analyses, aducanumab plus supportive care versus supportive care alone. We specified standard aducanumab cost-effectiveness analysis Outcomes, incremental cost per quality-adjusted life year (QALY) and equal-value of life year (evLY) gained, and the traditional Time horizon, lifetime.

While the QALY, the academic standard in cost-effectiveness analysis for measuring how well all different kinds of medical treatments lengthen and/or improve patients’ lives, may be familiar to some readers, the evLY gained may be less so. To complement the use of the QALY, the evLY gained equally measures gains in length of life, regardless of the treatment’s ability to
improve patients’ quality of life during life extension. In other words, if a treatment adds a year of life to a vulnerable patient population – whether treating individuals with cancer, multiple sclerosis, diabetes, epilepsy, or a severe lifelong disability – that treatment will receive the same evLY gained as a different treatment that adds a year of life for healthier members of the community.\textsuperscript{12} By understanding a treatment’s cost per evLY gained, as well as its conventional cost per QALY gained, policymakers are able to take a broader view of cost-effectiveness and be reassured that they can consider information that poses no risk of patient discrimination. The decisions made to estimate lifetime differences in health (intervention versus comparator QALYs and evLYs), the cost-effectiveness Outcomes, are featured in the next section of this narrative.

Before turning to two noteworthy decisions made in the scoping phase, we highlight a decision where we relied on clinical expertise when modeling aducanumab over a lifetime Time horizon (beyond the observed duration in the pivotal trials). Once aducanumab treatment is initiated, questions remain related to when one may terminate aducanumab treatment in patients. In discussion with clinical experts, our team decided that despite limited evidence from the trials, those who initiate aducanumab and do not experience severe adverse events would likely not stop the treatment upon progression to moderate AD. Conversely, due to the unknown effect and the intravenous route of administration, clinical experts agreed that continuing aducanumab within severe AD would be unlikely. Thus, we decided to discontinue aducanumab treatment in model simulations once patients transitioned to severe AD. The impacts of this treatment stopping rule were tested by way of scenario analyses (i.e. continuing aducanumab treatment until death).
Noteworthy decisions made in the aducanumab scoping phase included: specifying the model structure; and specifying the analytic perspective and whether (and if so, how) to include caregiver effects.8

Choice of Model Structure

Cost-effectiveness analyses can be developed using different model structures to simulate the clinical events and transitions that occur over the specified time horizon. A key model structure choice for the aducanumab evaluation was between using a state-transition model (e.g. Markov model) and a discrete event simulation. A state-transition model has mutually exclusive and exhaustive health states that are dependent on the clinical area and the model then uses evidence of the transitions between health states. A discrete event simulation instead models specific events and generally tracks history at the individual level. Both model types appeared feasible in addressing the study objective. According to best practice guidelines, a state-transition model should be used when the clinical trajectory can be represented with a manageable number of health states that incorporate all characteristics important to the decision problem, including the relevant patient history.3 Discrete event simulation should be considered for a variety of reasons including when interactions between individuals or clusters impact cost or health outcomes and when the order of events can vary across individuals and impact cost or health outcomes.3

After scoping discussions with clinical experts, patient advocacy groups, and the aducanumab manufacturer, we gave low priority to tracking interactions or patient history beyond those characterized by AD progression in estimating the cost-effectiveness of aducanumab. AD is progressive with rare examples of individuals improving over time.
Further, aducanumab does not have evidence to suggest reversing the course of disease, suggesting limited impact of atypical patient progression paths. Clinical experts noted measurement challenges around AD progression, but when including mild cognitive impairment due to AD, suggested that the four common AD progression states (MCI due to AD, mild AD, moderate AD, and severe AD) alongside dwelling status (home versus institution) had strong correlation with patient- and caregiver-important outcomes and health care utilization. Further granularity beyond progression state and dwelling status, for example, time spent in any given health state, was not anticipated to be a driver of model outputs given a lack of evidence suggesting strong interactive effects with patient outcomes or cost. For the above reasons and others, we chose a state-transition Markov model.\(^3\)\(^8\)

Our model choice was consistent with preceding AD published cost-effectiveness models where the mutually exclusive and exhaustive health states often included MCI due to AD, mild AD, moderate AD, severe AD, and death.\(^{13-15}\) A recent systematic review evaluated economic evaluations for dementia and demonstrated that the majority of studies used a Markov model with the same structure we undertook to represent disease progression.\(^{15}\) The model health states are consistent with ranges of Clinical Dementia Rating Scale Sum of Boxes (CDR-SB).\(^{16}\) The CDR-SB is an instrument that assesses three domains of cognition (memory, orientation, judgment/problem-solving) and three domains of function (community affairs, home/hobbies, personal care) based on an interview with the patient or caregiver. Our choice required an underlying assumption of a state-transition Markov model, namely that patients within each health state have relatively homogenous cost-effectiveness intermediate outcomes (e.g. health care resources, caregiver resources, quality of life, and probability of death given age). This assumption was supported by discussions with clinical experts and by evidence that included quantitative relationships between the five health states and cost-effectiveness.
intermediate outcomes. Finally, we note that our choice of this five-state Markov model drove model evidence needs, namely, the probability of moving from one health state to another (for the intervention and comparator).

Analytic Perspective(s)

A perspective in a cost-effectiveness analysis determines what resources are included in the analysis. For example, if your perspective was the health care system perspective, you would include costs related to the health care system. You would not include costs that influence sectors outside of healthcare (e.g., criminal justice, education, etc.). The Second Panel on Cost-Effectiveness in Health and Medicine, a reputable academic voice for US cost-effectiveness analysis recommendations, is clear in their stance on recommending two analytic perspectives be included in cost-effectiveness analyses whenever possible: one based on a health care system (sector) perspective and another based on a societal perspective. The Second Panel’s Impact Inventory (See eTable 1 in NEUROLOGY/2021/177399), the health care system perspective includes all medical and pharmacy costs paid by third parties or patients, long-term care costs for the patients, and all future related and unrelated medical and pharmacy costs. Additionally, patient health outcomes are typically incorporated in the health care system perspective.

The societal perspective includes the costs from the health care system but also includes informal health care costs (e.g. patient time costs or unpaid caregiver costs) and non-health care system costs (e.g. productivity-related costs, education, environment, housing, etc.). Further, health outcomes of the caregiver(s) may be incorporated in this broader perspective in addition to the patient health outcomes included in the health care system perspective. It is
not typical to include health or economic impacts of the caregiver within health technology assessments, but it is an emerging area of research.\textsuperscript{17}

For the aducanumab evaluation, we opted to include two co-equal (co-base-case) perspectives, the health care system and the societal perspectives, due to the substantial impact that an effective treatment for AD might have on outcomes beyond the health care sector. Owing to the potential impacts that an Alzheimer’s disease modifying therapy may have on those beyond the patient, we chose to not only include potential productivity impacts on patients but also include caregiver cost and health impacts. Although a reasonable reaction to such decisions from the researcher perspective may be to “run it both ways,” and to present the corresponding findings, opting for two co-base cases can suggest a wider range of value-based prices (prices derived based on the modeled health gains rather than based on the manufacturer asking price). Given aducanumab’s treatment effect was uncertain and not considered a cure, the incremental cost-effectiveness findings from the societal and health care system perspectives remained within a tight range. In situations where the stated perspective leads to wide ranging findings, we recommend leaning on guiding principles such as a value assessment framework to help interpret the findings alongside their potential impacts on value-based pricing.\textsuperscript{18}

\textbf{Contribution Area #2: Extrapolating Beyond the Available Evidence}

The time horizon for the cost-effectiveness analysis is often longer than the follow-up period from the pivotal trial or from other available evidence. This involves extrapolating the evidence beyond what is available for the duration of your time horizon. Clinical researchers’
contributions in this area are important, to ensure that these extrapolation assumptions are plausible and defensible to promote the accuracy of the results. Noteworthy decisions made in the model analysis plan phase of the aducanumab analysis included how to estimate the lifetime health gains (QALY and evLY gains, the cost-effectiveness outcomes) given the available trial evidence.\textsuperscript{19} Modeling the lifetime health gains associated with aducanumab involved notable decisions including: 1. quantifying the evidence-based benefits and harms of aducanumab versus supportive care; 2. translating evidence-based benefits and harms into survival and quality of life utility scores, the two components of QALYs and evLYs; and 3. forecasting benefits and harms over a lifetime.

**Quantifying Aducanumab Benefits and Harms**

A fundamental step in estimating an intervention’s cost-effectiveness is to first quantify the comparative effectiveness and harms of the intervention versus its comparator(s) using patient-important outcomes. The full list of patient-important outcomes and the comparative clinical effectiveness and harms of aducanumab are presented elsewhere.\textsuperscript{9} From this comprehensive analysis, we used the patient-important outcomes that translated to QALY or evLY health differences. Multiple patient-important benefits and harms may be used in cost-effectiveness analyses, but in the aducanumab case, there was one key treatment-associated benefit and one key harm. The key trial-based benefit and harm outcomes for the aducanumab CEA were the hazard ratio for progressing to a worsening health state of dementia (benefit) and the probability of amyloid-related imaging abnormalities (ARIA-E and ARIA-H) (harm). We note that the key trial-based benefit is directly tied to the choice of model structure. Therefore, clinical expertise is helpful in not only decisions (and corresponding assumptions) of model structure but also in fitting a treatment’s measured benefit(s) to the model structure.
The hazard ratio for progressing to a worsening state was not a primary or secondary measure from EMERGE or ENGAGE. Upon request, the manufacturer submitted the intention-to-treat aducanumab hazard ratio for transitioning from MCI to mild dementia due to AD for EMERGE (supplied as academic in confidence), but we did not receive a comparable estimate from ENGAGE. We made decisions informed by clinical and other stakeholders that were consistent with good modeling practices, namely, we decided to pool the key treatment benefit across two trials over using evidence from the single, more favorable trial. We judged that there were insufficient reasons to discount the validity of the ENGAGE results and that usual practice would therefore entail pooling data from two concurrent pivotal trials using the same patient eligibility criteria and same outcome measures. The quality of evidence increases and precision decreases when one meta-analyzes more than one comparably designed trial.\(^{20}\)

Given we did not have a comparable hazard ratio (or its uncertainty) from ENGAGE, we used the proxy of the relative change in CDR-SB. We acknowledge the shortcomings of pooling evidence with the use of a proxy measure. Clinical guidance was helpful in discussing the proxy measurement options from ENGAGE. The relative change in CDR-SB was chosen as the best option given it was the primary outcome in the trial and its comparability to the hazard ratio for transitioning from MCI to mild dementia, health states that were also defined by CDR-SB ranges.

The probability of ARIA-E and ARIA-H was estimated by pooling evidence from ENGAGE and EMERGE trials. Based on stakeholder feedback, the act of pooling across the two comparably designed trials was considered as the best available evidence approach for estimating this harm in the model. Alongside background transition probabilities for supportive care alone, other patient-important outcomes (e.g. added time spent in a community vs. long-
term care setting, health impacts on caregivers) were based off aducanumab’s potential to slow the progression of disease and were derived from other published literature.

**Translating Aducanumab Benefits and Harms**

Once designed and programmed, the health-state Markov model allowed for the translation of aducanumab’s evidence-based benefits and harms into corresponding model outcomes (difference in QALYs and evLYs for aducanumab plus supportive care versus supportive care alone). We measured differences in QALYs and evLYs by specifying health-related quality of life utilities for each model health state (and treatment strategy) and by specifying the probabilities of death from each health state (and treatment strategy). As mentioned previously, the societal perspective not only included utilities for patients but also for a primary caregiver. Fortunately, published literature sources were available to specify all health state utilities for the patient and decrements in utility (disutility) associated with the caregiver. Further, published literature had estimated the disutility and duration related to ARIA events. To generalize beyond the aducanumab case in terms of translating trial benefits and harms into common CEA measures, we recommend that CEA-informed researchers be involved in the trial design team. We recommend careful collection of instruments within trials that have direct mappings to US utility scores such as the European Quality of Life Five Dimension (EQ-5D) so that utility estimates by health state are consistent with the trial setting and population.

**Forecasting Aducanumab Benefits and Harms**
The final decisions in estimating lifetime health gains surround forecasting these patient-important outcomes beyond the duration of the trials to mirror the time horizon in the cost-effectiveness analysis (lifetime in the aducanumab case). We did not have enough observed transitions in either trial to estimate hazards for transitions beyond MCI to mild AD (e.g. mild to moderate, or moderate to severe, or severe to death) because the majority of the trial participants being in earlier stages of disease (e.g., MCI due to AD). Due to lack of evidence for estimating the other aducanumab hazard ratios, we relied on clinical expert guidance and corresponding assumptions detailed in the CEA manuscript. We tested such assumptions by way of sensitivity and more optimistic and conservative scenario analyses. After consultation with stakeholders and reviewing evidence from other amyloid-targeted therapies, we assumed that the increased risk of ARIA was only during the first year of aducanumab treatment. Further, in alignment with the discontinuation due to adverse events reported in the trials, we assumed patients that experienced symptomatic ARIA would discontinue aducanumab treatment, although this assumption could change as more is understood about ARIA occurrence and management. Long-term observational studies and ongoing conversations with clinical experts could aid in reducing the uncertainty in ARIA-related assumptions.

**Contribution Area #3: Characterizing and Presenting Uncertainty**

Two general forms of uncertainty may be characterized in cost-effectiveness analyses: input (parameter) uncertainty and structural uncertainty. Model inputs such as the hazard ratio from MCI to mild are estimated as an average across the population. Characterizing input uncertainty is statistically handled through concepts consistent with confidence intervals for treatment effects. Modelling good practices suggest assigning plausible probability
distributions to model inputs where the distribution represents the uncertainty in the input.\textsuperscript{23} The impacts of each influential input’s uncertainty on model outputs is generally displayed by way of one-way sensitivity tornado diagrams. We have found these tornado diagrams are useful tools for cost-effectiveness analysis consumers in understanding the drivers of model results and how much results may change with the use of plausible ranges of inputs (See Figure 2 and eFigure 1 in NEUROLOGY/2021/177399).\textsuperscript{2} The impacts of all model inputs on model output uncertainty can be displayed using cost-effectiveness acceptability curves or by selecting different cost-effectiveness thresholds and displaying the likelihood that the intervention is cost-effective.

We suggest using scenario analyses as the way to capture influential assumptions or model structural elements. In the aducanumab cost-effectiveness analysis, we highlighted optimistic and conservative assumptions that influenced the deterministic results. In optimistic scenarios, we modeled treatment benefits consistent with only the EMERGE trial. In conservative scenarios, we modeled treatment benefits that did not extrapolate beyond the evidence shown in MCI and mild disease. Clinical experts were helpful in establishing plausible lifetime effectiveness bounds for the optimistic and conservative scenarios given the available evidence. These scenarios help bound an understanding of aducanumab’s cost-effectiveness and may be weighted by policymakers based on their interpretation of the evidence.

**Conclusions**

Cost-effectiveness analyses are an important starting point for population-level decision making and negotiations around the fair price of health interventions.\textsuperscript{24} The act of specifying the objective and the number of model choices, assumptions, and evidence may be the most
important step in cost-effectiveness as it allows for structured engagement and conversation about the evidence, assumptions, and corresponding effects on findings. Cost-effectiveness analysis is therefore foundational in bringing together considerations around comparative benefits, harms, and costs of different treatment options and is uniquely suited to support discussions of whether a price aligns well with the overall benefits to patients. The case of aducanumab provides ample fodder for such engagement and conversation.\textsuperscript{25-28} There is particular uncertainty in interpreting early evidence on interventions, and yet cost-effectiveness provides a useful framework for making that uncertainty explicit through the key decisions and assumptions in the model, and allows for the testing of uncertainty through sensitivity and scenario analyses. Aducanumab represents a situation in which patients, clinicians, insurers, and policymakers all will be making decisions with tremendous consequence, and the key decisions and assumptions in aducanumab cost-effectiveness analysis reflect how important it is for clinical expert input to be incorporated in the design and interpretation of the model and its results.

2. Cost-Effectiveness and Value-Based Pricing of Aducanumab for Patients with Early Alzheimer’s Disease. (NEUROLOGY/2021/177399).


