INTRODUCTION

Objectives and methods

OBJECTIVE

Our objective was to evaluate how different sources for estimating disease progression impact simulated long-term outcomes.

METHODS

AD ACE Overview

The AD ACE is a Microsoft Excel-based discretely integrated condition-event (DICE) simulation and was developed in accordance with Modeling Good Research Practices disseminated by the International Society of Pharmacoeconomics and Outcomes Research (ISPOR).1

It incorporates intercorrelated predictive equations that have been derived mainly from large and representative datasets and clinical trials.

These equations describe disease progression through the evolution of biomarkers of AD and various relevant patient-level scales: cognitive, behavior, function, and independence.

The AD ACE considers interrelated clinical, epidemiologic, and economic outcomes.

Along with disease progression, the primary model outputs include patient quality of life, costs of care, and risks of institutionalization and mortality.

Figure 1. Influence diagram outlining the key relationships in the AD ACE simulator

Model Description

We simulated disease progression over 15 years using the AD-ACE simulator in a cohort of 1,334 normal cognition or mild cognitive impairment (MCI) patients from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) with Mini-Mental State Exam (MMSE) scores ≥25.

Predicted changes in cognition and behavioral functions were simulated over time using two sets of equations:

1. Equations based on ADNI data, which consists of individuals from normal cognition to mild AD with few observations in more severe stages.

2. Published equations from the Health Economics in Alzheimer’s Disease II (AHEAD) model, which developed predictive data from patients already diagnosed with mild-to-severe AD.

A switch between the ADNI and AHEAD equations were triggered as patients progressed to more severe stages of AD (see Figure 2).

- Comparability of reported measures (e.g. ADAS-Cog 11 vs. ADAS-Cog 13) between ADNI and AHEAD equations were carefully assessed and necessary adjustments were made to equation results to maintain consistency in the reported AD ACE outcomes across all disease stages.

- In a sensitivity analysis, several thresholds for switching between ADNI-based and AHEAD equations were tested and the impact on progression and need for institutional care was subsequently studied.

- Switch criteria and disease progression rates over the range in which they overlap (i.e. mild to moderate AD).

Three sources to estimate disease progression rates:

- Published equations from large and representative datasets and clinical trials.

- Published equations from the ADNI longitudinal datasets.

- The flexibility to switch between ADNI and AHEAD equations enables AD ACE to simulate the full spectrum of AD patients in various disease stages.

RESULTS

A sensitivity analysis was performed to study the impact of various MMSE-based equation switch thresholds (10, 15, 20, 25, and 30) on disease progression and institutional care.

When ADNI equations were used in patients from baseline until development of moderate AD (MMSE = 15) and AHEAD equations subsequently, it took 13.9 years to reach a population mean MMSE of 10 (see Figure 3a).

This value was stable when the threshold for switching between equations varied between MMSE of 15 and 30 after 10 years.

Accordingly, fewer patients required institutional care with the combined equations (98%) than using ADNI (84%) or AHEAD equations (74%) alone at the end of 10-year time horizon.

The mortality rate turned off in all arms in order to better track patients’ long-term disease progression independent of patient’s survival risk.

Figure 3. Simulated trajectories of mean a) MMSE and b) NPI10 scores for varying combinations of ADNI and AHEAD equations over a range of multiple MMSE score thresholds

DISCUSSION

Equations based on ADNI data and those from AHEAD predict faster progression than the combination of the two sources, potentially overestimating the fraction of patients requiring institutional care.

This sensitivity analyses shows that a combination of the ADNI and AHEAD equations offers a better prediction of disease progression for AD patients across all disease stages.

CONCLUSION

The flexibility to switch between ADNI and AHEAD equations enables AD ACE to simulate the full spectrum of AD patients in various disease stages.

The ADNI and AHEAD equations were derived independently from completely separate datasets, but the results of this sensitivity analysis shows that they offer similar predictions of disease progression rates over the range in which they overlap (i.e. mild to moderate AD).

REFERENCES