Supplemental material 3 corresponding to manuscript: "Cost-effectiveness Models for Alzheimer's disease and related dementias: IPECAD Modelling Workshop Cross Comparison Challenge". See www.ipecad.org.

Comparison of Cost-Effectiveness/Disease Progression (Health Economic) Models in Alzheimer's Disease

NETWORK Meeting, 2020

Work plan 2020-07-27

1. INTRODUCTION

Trust and confidence are critical to the successful use of decision-analytic health care models. The aim of this meeting is to improve the transparency and trust aligned to use of health economic models in the context of Alzheimer's disease (AD). This will be achieved through ongoing development of methods, improved reporting standards, and related good practice within the field of decision-analytic modelling in the area of AD. The key objective of this upcoming meeting is to receive submissions on AD modelling aligned to the challenge/scenarios set out, and to systematically examine cross-model differences in predicted outcomes, with structured discussion in relation to model design choices and parameterization. The meeting is based on a reference case benchmark scenario (and requested output matrix) – developed through prior discussion – that can be run in multiple health economic models of Alzheimer's Disease (AD), and which will allow comparison of model predictions and facilitate identification of possible factors explaining the range of and heterogeneity across modelling and simulation outcomes.

2. METHODS

2.1. GENERAL OVERVIEW

- The meeting will use the work of Eddy at al [i] as a foundation/platform for the comparison of submitted models. The core of the meeting will be based on cross-validation methodology comprising:
    - Run a similar scenario in different models that address the same decision problem.
    - Examine the differences among the results and explore/identify their causes.
    - The reference case/benchmark modelling scenario (in development here) is that which has been determined prior to the meeting, through consultation, by expert opinion, and finalized by a subgroup of the IPECAD 2019 workshop participants and IPECAD Modelling Group.
- Practical approach:
    - The reference case/benchmark modelling scenario, and reporting requirements (i.e. this document) are shared/circulated prior to the meeting.
    - Groups/Analysts (Contributors) run their model by themselves with the specific scenario and share their outcomes in the pre-defined format.
    - Submissions (results) will be shared in confidence.
    - IPECAD Modelling Group / meeting organisers will prepare a simple descriptive comparison of all submitted model's results and will share with all involved (Contributors / Organisers) in the meeting (shared in confidence).
    - In advance of the meeting, several teleconferences will be hosted (by Organisers) with all Contributors to discuss the descriptive comparison (prepared/drafted). This preparatory discussion will be used to initiate the wider process of examining

differences in submissions, which will from the core component of the scheduled Network meeting. It is important to acknowledge, at the outset, that differences in model outputs do not indicate one model being more correct than another – the purpose is to illustrate the impact of design choices, and inputs, on model outputs and thereby improve transparency and acceptability.

- o The workshop organizers will use these preparatory teleconferences to discuss progress as well as to prepare the findings, in order to present them at the scheduled Network meeting.

2.2. REFERENCE CASE / BENCHMARK MODELLING BASE-CASE SCENARIO

- Population:
  - o A. Persons with AD-type MCI (analyst to detail diagnostic criteria used, e.g. on use of biomarkers).
  - o B. Persons with AD-dementia (analyst to detail diagnostic criteria).
  - o Starting age 70 years
  - o In a clinical setting (typically memory clinic), with patients already identified for treatment (no procedures or costs for diagnostics to be included)
  - o Usual care (e.g. incl. ChEI in AD-dementia) is applied in the model's control strategy.
- Intervention:
  - o Disease-modifying intervention.
  - o Resulting in 30% reduction on the progression (by adjusting conversion rate or cognitive outcome progression rate with a rate or hazard ratio of 0.70, or otherwise comparable intervention effect depending on model structure and parameters) for A. conversion from MCI to AD-type dementia, or B. progression in dementia.
  - o A. In MCI state, and treated until conversion to dementia, or B. in dementia state treated until moderate dementia; for a maximum of 5 years (both in A and in B). This means the treatment is started at model entry and will be provided for the next 5 years or shorter if conversion to dementia (in scenario A) or progression to moderate dementia (in scenario B) occurs.
  - o 10% intervention discontinuation per year.
  - o Intervention cost $5000/year.
- Time horizon(s): 10 years and lifetime
- Discount rate costs/QALYs: 3.5%
- Half cycle correction (if applicable i.e. if Markov type cycle duration used)
- The model's deterministic outcomes will be used

2.3. MODEL OUTCOMES TO BE REPORTED:

- See table 1 and 2
- Model methods:
  - o Relevant model characteristics, assumptions and operationalizations (see table 3)
  - o Applied cost and QALY input estimates vectors
- Comparators: intervention, no intervention
- Time horizons: 10 years:
- Mean person-years:

- o Alive
- o In MCI
- o In mild dementia (some harmonization is required on definition of mild dementia, suggest practical mapping method (e.g. mild dementia = CDR1 or MMSE range 20-25)
- o In Moderate dementia (as above, CDR2 or MMSE 10-19)
- o In Severe dementia (as above, CDR3 or MMSE<10
- o On intervention
- o Full-time care or living in institutionalized setting
- Cohort annual state-trace (proportion of patients in states MCI/mild/moderate/severe/death by year since baseline)
- Cost/QALY outcomes:
  - o Mean discounted costs (disaggregated intervention, direct medical, direct nonmedical costs)
  - o Mean discounted QALY (patient only)
  - o Incremental cost-effectiveness ratio (ICER)

2.4. OPTIONAL STEPS
- Dependent on available time further requirements are (sorted by priority).
- Use of standard/reference case mortality inputs (to be specified/determined).
- Sensitivity analysis on different model parameters (e.g. starting age, intervention effect etc.).
- Harmonize population-specific model inputs where possible
  - o costs
  - o utilities
  - o convert to dollar specific index year
  - o use same NACC input data to produce and compare the disease-progression outcomes
  - o Test if models are differently sensitive to inputs (e.g. intervention effect)
- Start in pre-clinical population age 65 (might require adjusting the model)
- Distribution of men/women corresponding to the studied population, or alternatively results reported separately for men and women or set reference proportions/distributions (e.g. 50/50).
- Specify the MCI population in terms of early/late MCI and other factors (to be specified/determined).
- External validation of registry: predict NACC and ICTUS observed progression data.

2.5. ANALYSIS

- All single-point outcomes will be tabulated (i.e. table 1a) and the variance will be described.
- Proportions of the simulation sample across the states (i.e. table 2b) will be plotted over time and compared visually. As there are no established and widely accepted methodology for evaluating concordance in health-economic simulation modelling, this visual test will not be quantified.

2.6. REPORTING

- If the data allow it, the aim is to write up the findings from the meeting and to submit a manuscript to an international peer-reviewed journal for publication.
- Likewise, to submit an output to an international conference for an oral/poster (e.g. AAIC, CTAD, ISPOR, others: 2021 meetings)

Table 1: template table to report cumulative outcomes over 10-year time horizon (mean per person).

	Control	Intervention
Cumulative person-years over 10-year time horizon (mean per person)		
Alive		
MCI		
Mild dementia		
Moderate dementia		
Severe dementia		
On intervention		
Full-time/institutionalized care		
Cumulative discounted costs over 10-year time horizon (mean per person)		
Intervention		
Direct medical		
Direct non-medical		
Cumulative discounted QALYs over 10-year time horizon (mean per person)		
Patient		
Informal carer		
ICER	n/a	
Please feel free to list other outcomes at the end of this table (list item and unit)		
…		

Table 2a: template table to report proportion of persons in each state over time in the control strategy.

Year	MCI	Mild dementia	Moderate dementia	Severe dementia	Death
0	1	0	0	0	0
1					
2					
3					
…					
25					

Table 2b: same as 2a for intervention strategy.

Year	MCI	Mild dementia	Moderate dementia	Severe dementia	Death
0	1	0	0	0	0
1					
2					
3					
…					
25					

Table 3: reporting table for model characteristics, assumptions and operationalizations.

Characteristic	Description
Study population at baseline	
Age (e.g. mean, sd, min/max, distribution)	
Sex (distribution)	
Syndrome (MCI or dementia)	
Aetiology (AD, mixed, etc.)	
APOE status (e.g. e4 carriers, homozygotes, heterozygotes)	
Biomarker status (e.g. amyloid positive, AT(N))	
Care setting (e.g. community, memory clinics, residential care setting)	
Severity distribution (as applicable)	
…	
Model settings (aligned with scenario)	
Time horizon	
Discount rate (cost/Qalys)	
…	
Intervention (aligned with scenario)	
Annual intervention cost	
Intervention effect[1]	
Waning or persistence of effect	
Intervention stopping rule	
Intervention discontinuation	
…	
Model data (as applicable)[2]	
Progression/conversion rates	
Mortality	
Institutionalization risk	
Costs & utility inputs	
…	

[1] This includes a description of the treatment continuation effect (i.e. the effect on natural progression after treatment has stopped). This can for example be a parallel effect, the same relative effect, back to natural progression (i.e. control strategy's progression), or a combination.

[2] Table with specific inputs can be provided separately (e.g. relative risks or age-specific mortality table)

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[i] https://www.ispor.org/docs/default-source/resources/outcomes-research-guidelines-index/model_transparency_and_validation-7.pdf?sfvrsn=24168dfb_0