Detailed planning

Herewith we provide a detailed instruction for modeling groups for the cross-comparison, structured alongside a timeline toward the workshop meeting on 13 and 14 April 2023 in Stockholm (and virtual meeting to be planned around end of April 2023). Attached to this instruction is a benchmark scenario description containing the introduction and methods for the cross-comparison benchmark scenario.

- **December-January:**
    - Organizers send a detailed instruction and summary tutorial video for the cross-comparison on how to prepare for the workshop (omitting details on how to implement the Benchmark Scenario as that is up to each participant).
    - Participants study the Benchmark Scenario document (starting age, sex, MCI due to AD diagnosis, memory clinic setting, treatment costs, treatment waning, U.S. mortality, utility and costs, and other details). They consider adjustments to their model such that it adheres to the Benchmark Scenario, without changing the fundamental design of the model. Supportive information for adhering to a U.S. setting can be found below.
    - Participation is only possible if a model reflects the Benchmark Scenario. Participants provide feedback to the Organizers in case of any questions or uncertainties regarding implementing the Benchmark Scenario into their model.
    - Participants feedback any issues they encounter on these steps.
    - If considered necessary, Organizers will organize teleconference(s) with the Participants to discuss any issues and adjust/update the methods (Benchmark Scenario, pre-defined outcomes, comparison method, etc.).
- **February-March:**
    - Participants implement the DMT effect into their model.
    - Participants run their model themselves, applying the Benchmark Scenario.
    - Participants share their model Outcomes in the pre-defined format detailed in the Benchmark Scenario document with the Organizers in confidence.
    - If considered necessary, the Organizers will organize teleconference(s) with the Participants to discuss progress as well as to prepare the findings, in order to present them at the scheduled Workshop.
    - Organizers will prepare a simple descriptive comparison of all submitted model's Outcomes and will share this with all involved Participants in confidence.
    - Participants are willing to share their model Outcomes as detailed in the Benchmark Scenario document for the Organizers to make them publicly available. Organizers aim to describe and discuss the results from the model cross-comparison in a scientific manuscript and submit it to an international

peer-reviewed journal or conference for an oral/poster. Participants who met the conditions for participation qualify for authorship (max. 2 authors per modelling group).

- **April:**
    - Participants and Organizers take part in one of the two scheduled Workshop meeting: (1) face-to-face meeting planned for 13 and 14 April 2023 in Europe (venue to be decided); (2) virtual meeting to be planned around April 2023.

Benchmark scenario

IPECAD Modeling Workshop 2023 Cross Comparison Challenge on Cost-Effectiveness Models in Alzheimer's Disease and related dementias

Background information for workshop participants

INTRODUCTION

World-wide nations are challenged with deciding upon the allocation of scarce healthcare resources to ensure people with Alzheimer's disease (AD) have timely access to effective interventions. Mathematical model-based economic studies support policy discussions on reimbursement. Such models implement the results from clinical trials typically extrapolating short-term clinical data on effectiveness results (e.g., effects on biomarker targets and cognitive scale) to model the lifetime impact on patient-relevant outcomes (function, care use and mortality). The models do so through combining various sources of evidence, such as data from trials, disease registries and cohort studies. Transparency and credibility of these models provide key support for the decision makers who rely on them [Oliver, 2014] and modeling can assist the timely access to new interventions for people living with AD. Unexplained differences between the findings from AD models could jeopardize their credibility and lead to suboptimal decisions (e.g., reported in the field of abdominal aortic aneurysm screening [Campbell, 2007; Sogaard, 2012]).

Comparative modeling could increase confidence in models if similar results are observed [Eddy, 2012; AdViSHE, 2016]. A survey from the IPECAD modeling workshop in 2021 found that participants indicated a lack of empirical evidence for extrapolating short-term cognitive trial outcomes to long-term outcomes (e.g., function, care needs, and mortality). Clinical trials are not primarily designed to provide input to health-economic models, and health-economic models are usually based on evidence not designed to match trial outcomes. The IPECAD modeling steering group identified several challenges:

- Endpoints and scales: health-economic models are developed from observational studies that often include different endpoints and scales compared to clinical trials. Mapping between scales used in the trials and scales used in models can introduce considerable uncertainty.
- Multiple effect domains: Treatment effects can in health-economic models be represented either through a single domain (e.g., cognition), or on multiple domains (e.g., cognition, function and behavior). Decision on which effect domains to include are often made post-hoc based on known trial outcomes. If effects are represented on multiple domains, the method for translating trial efficacy data into effects applied in the health-economic model becomes increasingly complex and sensitive to methodological choices. See figure 1 for various possible assumptions on causality between multiple domains. Further, the use of composite endpoints carries the additional risk of spurious correlations between treatment effects and health-economic outcomes. It is plausible that the treatment may primarily affect one subdomain of the

composite endpoint, while the correlation with costs and quality of life outcomes may be mainly driven by other subdomains.

- Estimating treatment efficacy: There are important differences between standard biostatistical methods for clinical trial data and the methods used in health-economic modeling. Health-economic models often categorize patients into disease states rather than utilizing clinical scales as continuous variables. This facilitates the analysis of disease progression as well as calculation of costs and utilities. Estimating treatment effects for integration in health-economic models therefore involves post-hoc analysis of the trial data outside of the statistical analysis plan. This means that methodological decisions may not receive the same level of scrutiny and there may be higher risk of the methodological choices affecting the results.
- Patient population: Clinical trials are typically designed to optimize the probability of observing a treatment effect rather than to estimate the size of the potential treatment effect in a routine care population, (i.e., the typical focus of health-economic modeling). Translating the effects of a trial into a broader, real-world unselected population might be accomplished by an adjustment process (e.g., weighting the trial sample based on the covariate profile in relation to a general patient population). However, this has rarely been done in practice in past economic evaluations.

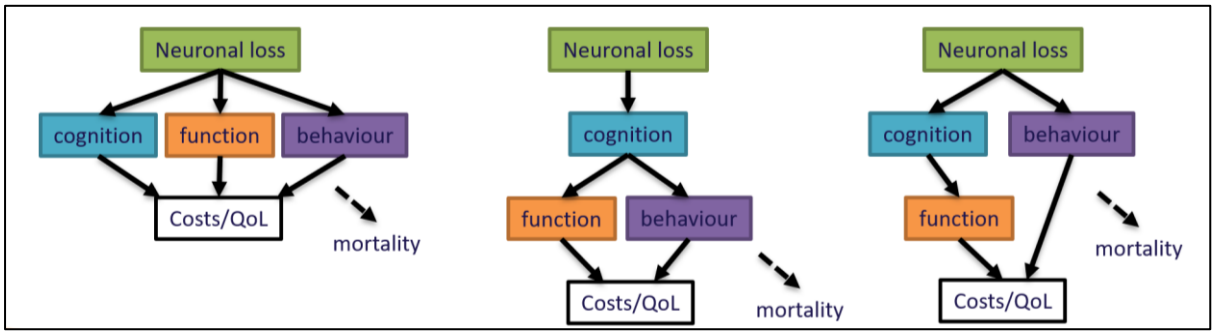

Figure 1: Three examples of assumed causality between outcome domains as a result of the treatment effect, used to extrapolate treatment effects beyond the trial period.

The **aim of this initiative** is to cross-compare outcomes from decision-analytic models for AD and related dementias that start in MCI and have implemented the same hypothetical trial efficacy estimates.

The following **research question** was set: What are differences in key health-economic outcomes across models that assess the cost-effectiveness of a hypothetical disease-modifying AD drug treatment, and what factors explain those differences?

This **focus of the workshop** is on the challenges of using trial outcomes in a decision model. Specifically, we seek to investigate the use of outcomes from short-term detailed trial efficacy evidence and their translation to long-term patient-relevant outcomes in a decision analytic framework. Our goal is to describe treatment implementation methods and discuss how they translate into differences in health-economic model outcomes (taking into account the specific model design, parameterization and model assumptions).

The present workshop uses a benchmark scenario that mimics the outcomes of a hypothetical DMT trial in terms of synthetic individual patient level as well as aggregated data on surrogate, symptom and biomarker outcomes. The timespan will be set over an 18-month period both for a placebo control and intervention arm using a hypothetical DMT in a population of persons aged 70 with a diagnosis MCI due to AD set at the first memory clinic visit in the U.S.

Only one base case scenario was used as a variety of (extreme) scenarios although informative was considered not feasibly within the limited available resources to the modeling groups.

METHODS

The design of the workshop and the initiative more broadly is based on guidelines for multi-model comparisons [den Boon, 2019] and the work by Eddy et al. [2012] on foundations for comparing models. The basic method entails first defining a-priori a research question; to be facilitated by the IPECAD modeling workshop steering committee (further referred to as organizers). Then the organizers identify modeling teams (participants) and – with participant agreement – set out a benchmark scenario which will be operationalized by participating modeling teams. Participants are invited to implement the benchmark scenario and run their model to generate standardized outcomes. The organizers will receive the modeling reports from participants and will summarize the model outcomes across the research groups. The summary will form a pre-read, for the workshop meeting held with the organizers and participants to discuss differences among the model outcomes and explore/identify their causes; thereby exploring and addressing the research question. A timeline is set by the organizers in advance of the process, with participants in agreement with the proposed timings.

MODEL IDENTIFICATION AND SELECTION

Models (participants) were identified from the following sources:

- Models represented by participants from the IPECAD workshop 2020 and 2021.
- From two systematics reviews of models, sub selection of models starting in MCI [Hernandez, 2016; Nguyen, 2018].
- Open call placed on ISPOR website forum [planned].
- Snowballing via invited modeling groups.
- Ad-hoc identified models from the Organizers.

We applied the following in- and exclusion criteria for model selection:

- Model reflects Alzheimer's disease or related dementia.
- Model purpose is health-economic (e.g., decision-analytic model, policy model, disease progression model with health and/or cost outcomes).
- Model starts in stage of mild cognitive impairment.

- Model contains a prediction of symptoms (cognitive and/or functional and/or behavioral), quality-adjusted life years and care costs (minimally medical care and social in terms of day care and institutionalized care).
- Model has possibility to reflect clinical setting (in terms of disease progression and mortality) and U.S. setting (in terms of cost, utility and background mortality estimates).
- Model has been published upon between 2005 or later.
- The combination 'model and modeling group' is independent. Independent model is defined as "a qualitative difference in structure or a fundamental difference in the representation or understanding of disease characteristics" [den Boon, 2019] as compared to other included models. As there is currently no best practice approach, we operationalized this as no adaptation, replication or duplication of in terms of model type (such as cohort state-transition, discrete event, or microsimulation), starting population (such as clinical diagnosis or biomarker-driven diagnosis), main disease progression source or method (such as NACC, SveDem, ADNI, or observed or parametrically derived transition probabilities), and/or mortality method. For example, models with an annual transition probability from MCI to dementia and dementia CDR-based mild/moderate/severe state transition model, regardless of the precise transition probabilities, is considered dependent. Independent modeling group is defined as the same head modeler or modeler's organization. If the combination 'model and modeling group' was dependent, the model version that best fit the benchmark scenario was chosen. 'Model and modeling group' independency will be judged by the members LJ, CG, RH, WH, AG of the Organizers. Opposite to recommended [den Boon, 2019], we allow dependent models (provided the modeling group is independent) as our goal is to increase model understanding rather than synthesize results for a policy question.

No internal or external validation will be used to limit model selection.

Modeling groups are invited if their model fulfills the in- and exclusion criteria, or can potentially fulfill it by making (small) adjustments to their model. They are invited using a save the date and invitation letter together with pre-specified protocol (see supplemental material 1 and 2 respectively).

- Model identification
  - Through systematic literature review
    - Review Hernandez (table 1, pre-selecting MCI population and 2005 or later): n = 2.
    - Review Nguyen (table A2.1a, pre-selecting MCI population and 2005 or later): n = 11.
    - Remaining after removing duplicates: n = 11.
  - Through participants previous workshops: n = 14.
  - Through open call ISPOR: n = x [planned].
  - Through snowballing invited modeling groups: n = 1.
  - Through ad-hoc identification by Organizers (including those who did not participate in 2020 workshop but who were on the 'reserve' list): n = 5.
- Remaining after removing duplicates:
  - n = 26
- Remaining after applying eligibility criteria:
    - N = x [planned]: AD or dementia health-economic model; purpose is health-economic; Starts with MCI; Prediction of symptoms, QALY, and care costs; clinical and U.S. setting (costs, utility, background mortality);
    - N = x [planned]: Independent model
  - N = x [planned]
- Accepted invitation:
    - No time
    - Not able to adjust model to U.S. inputs
    - No response
  - N = x [planned]
- Participated
  - N = x [planned]

Figure 1: Flow diagram for model identification and inclusion

REFINEMENT RESEARCH METHODOLOGY

Participants will be asked to provide feedback on the methods for cross-comparison (benchmark scenario and reporting tables); they will be given the opportunity to input. Participants will be asked to indicate alignment with the process and approach prior to modelling activity/input in terms of which adaptations they plan to make to adhere to the benchmark scenario. See supplemental material 3 and 4 for details.

HARMONISATION OF SCENARIOS, INPUTS AND OUTPUTS

The **Benchmark Scenario** consists of a description of the target population (operationalized as a set of standardized patients), setting and intervention efficacy. The latter is based on hypothetical trial outcomes, operationalized as synthetic individual patient-level data on a surrogate and secondary outcome (intervention AD DMT arm and control placebo arm) and summary tables/figures based on these synthetic data. All data reflects intention to treat and is assumed adjusted for conditional missingness as this is to be expected in practice. As recommended by the 2021 modeling workshop we standardized background mortality, (in)direct effect of treatment on mortality, specified treatment effect (symptomatic, disease-modifying or curative), expressed the treatment effect in units used as primary endpoints in a specific clinical trial, specified a standardized patient, and standardized health economic inputs. Each modeling group is free to implement this benchmark scenario into their model and adjust their model. However, participants are asked to maintain the model structure and 'deep' parameters to avoid model convergence. Modeling groups were free to decide upon the method for implementing the DMT such as the methods referred to in the introduction.

The target population **standardized patient** is defined as a person aged 70, male and female (modeled separately) with a diagnosis of amyloid confirmed AD-type MCI at his/her first visit at a memory clinic in 2020. Costs and effects related to diagnostics fall outside the scenario. The setting is a memory clinic in the U.S. The intervention strategy is a DMT in addition to standard of care. The control strategy is standard of care and placebo. The treatment effect and side effects are based on expert opinion by the IPECAD modeling workshop steering group. The treatment effect is considered 'disease-modifying'. The treatment is discontinued in 10%, which includes the discontinuation due to any adverse events (including ARIA-E). ~~including after symptomatic ARIA-E~~. Treatment is applied up to and including mild dementia. Treatment waning (i.e., no longer effective, but still provided) is assumed at 5% per year. It has an assumed list price ~~cost~~ of $5000 per year. Background mortality and consumer price index is set at year 2019 (pre-COVID19). Time horizon is 25 years and discount rate is 3.5% (both costs and effects). See tables 1-4 for the hypothetical trial in- and exclusion criteria, sample characteristics at baseline, efficacy outcomes and adverse events. See figure 2 for efficacy outcomes over time.

The **synthetic data** on baseline characteristics and efficacy for both the control and intervention arm of the hypothetical DMT trial are simulated from a variance-covariance matrix that was fitted to longitudinal data from a subsample of the ADNI participants that met our aforementioned eligibility criteria. For the intervention arm, a mean effect is assumed and applied to each individual. Adverse events were simplified by only reporting their mean and not including them in the individual patient level data. The synthetic trial is powered to

detect a minimum difference in CDR sum of boxed change from baseline of 0.25 based on the observed SD of 0.16 under the control condition, 80% power and 5% significance level. See supplemental 5 for details.

Suggestions to **reflect a U.S. setting** in terms of mortality, utility and cost estimates is provided in supplemental material.

Both the individual-patient level data as well as summary tables/figures are provided to all participants. If applicable, modeling groups are expected to apply mapping to translate the benchmark scenario outcomes to the outcomes used in their model. Each modeling group is asked to implement the benchmark scenario and share the model outcomes with all participants.

Table 1: Trial hypothetical in- and exclusion criteria.

Inclusion criteria: • Age between 55-85 • Objective impairment in episodic memory (based on Wechsler Memory Scale-IV Logical Memory II) • Amyloid positive* via amyloid CSF Amyloid Beta or amyloid PET • CDR = 0.5 • MMSE ≥ 24
Exclusion criteria: • MRI BASED confounding pathologies (e.g., acute or sub-acute hemorrhage) • Unstable dose of AChEI

* Definitions of positivity might vary across studies/measures/tools.

Table 2: Sample characteristics at baseline (standard deviation of the mean). Please be aware the benchmark scenario has a starting age of 70, opposite to mean baseline age of the hypothetical data.

	Control (SOC + placebo) n=654	**Intervention (SOC + DMT) n=654**	**p-value**
Age, mean (SD)	73 (6.7)	73 (6.8)	0.420
Female, %	42%	39%	0.400
Education (years), mean (SD)	16.5 (3.5)	16.1 (3.6)	0.079
ApoE e4/e4, %	18%	19%	0.620
CDR SOB, mean (SD)	1.71 (1.01)	1.70 (0.99)	0.870
MMSE, mean (SD)	27.4 (2.4)	27.2 (2.4)	0.350
ADAS-Cog13, mean (SD)	18.0 (7.4)	18.6 (7.3)	0.110
ADCOMS, mean (SD)	0.23 (0.12)	0.23 (0.12)	0.580
FAQ, mean (SD)	4.30 (6.72)	4.43 (6.73)	0.730
CSF ABeta24 (pg/mL), mean (SD)	718 (242)	705 (232)	0.340
CSF total tau (pg/mL), mean (SD)	311 (133)	325 (146)	0.067
CSF phosphorylated tau (pg/mL), mean (SD)	31 (15.0)	33 (16.5)	0.023
Amyloid PET SUVr centiloid, mean (SD)	68 (40)	72 (42)	0.041

Abbreviations: ADAS-Cog13, Alzheimer's Disease Assessment Scale-cognitive subscale; ADCOMS, AD Composite Score; CDR SOB, Clinical Dementia Rating sum of boxes; CSF, cerebrospinal fluid; DMT, disease-modifying treatment; FAQ, functional activities questionnaire; MMSE, Mini-Mental State Examination; PET SUVr, positron emission tomography standard uptake value ratio; SD, standard deviation; SOC, standard of care.

Table 3: Efficacy outcomes in terms of change from baseline after 18 months (standard error or the mean).

	Control (SOC + placebo) n=654	**Intervention (SOC + DMT) n=654**	**p-value**
CDR global, n (%)			0.463
-0.5 (from 0.5 to 0)	34 (5%)	54 (8%)	
+0 (from 0.5 to 0.5)	484 (74%)	473 (72%)	
+0.5 (from 0.5 to 1)	136 (21%)	127 (19%)	
+1.5 (from 0.5 to 2)	0	0	
+2.5 (from 0.5 to 3)	0	0	
CDR SOB, mean (SE)	0.84 (0.06)	0.59 (0.06)	0.004
MMSE, mean (SE)	-1.7 (0.2)	-1.1 (0.2)	0.021
ADAS-Cog13, mean (SE)	3.8 (0.3)	2.2 (0.3)	0.000
ADCOMS, mean (SE)	0.12 (0.01)	0.08 (0.01)	0.000
FAQ, mean (SE)	2.6 (0.3)	1.9 (0.3)	0.058
CSF ABeta24 (pg/mL), mean (SE)	-36 (6)	267 (6)	0.000
CSF total tau (pg/mL), mean (SE)	6.8 (2.3)	-125.7 (2.3)	0.000
CSF phosphorylated tau (pg/mL), mean (SE)	0.2 (0.3)	-20.1 (0.3)	0.000
Amyloid PET SUVr centiloid, mean (SE)	5.9 (0.9)	-45.3 (0.9)	0.000

Abbreviations: ADAS-Cog13, Alzheimer's Disease Assessment Scale-cognitive subscale; ADCOMS, AD Composite Score; CDR SOB, Clinical Dementia Rating sum of boxes; CSF, cerebrospinal fluid; DMT, disease-modifying treatment; FAQ, functional activities questionnaire; MMSE, Mini-Mental State Examination; PET SUVr, positron emission tomography standard uptake value ratio; SE, standard error; SOC, standard of care.

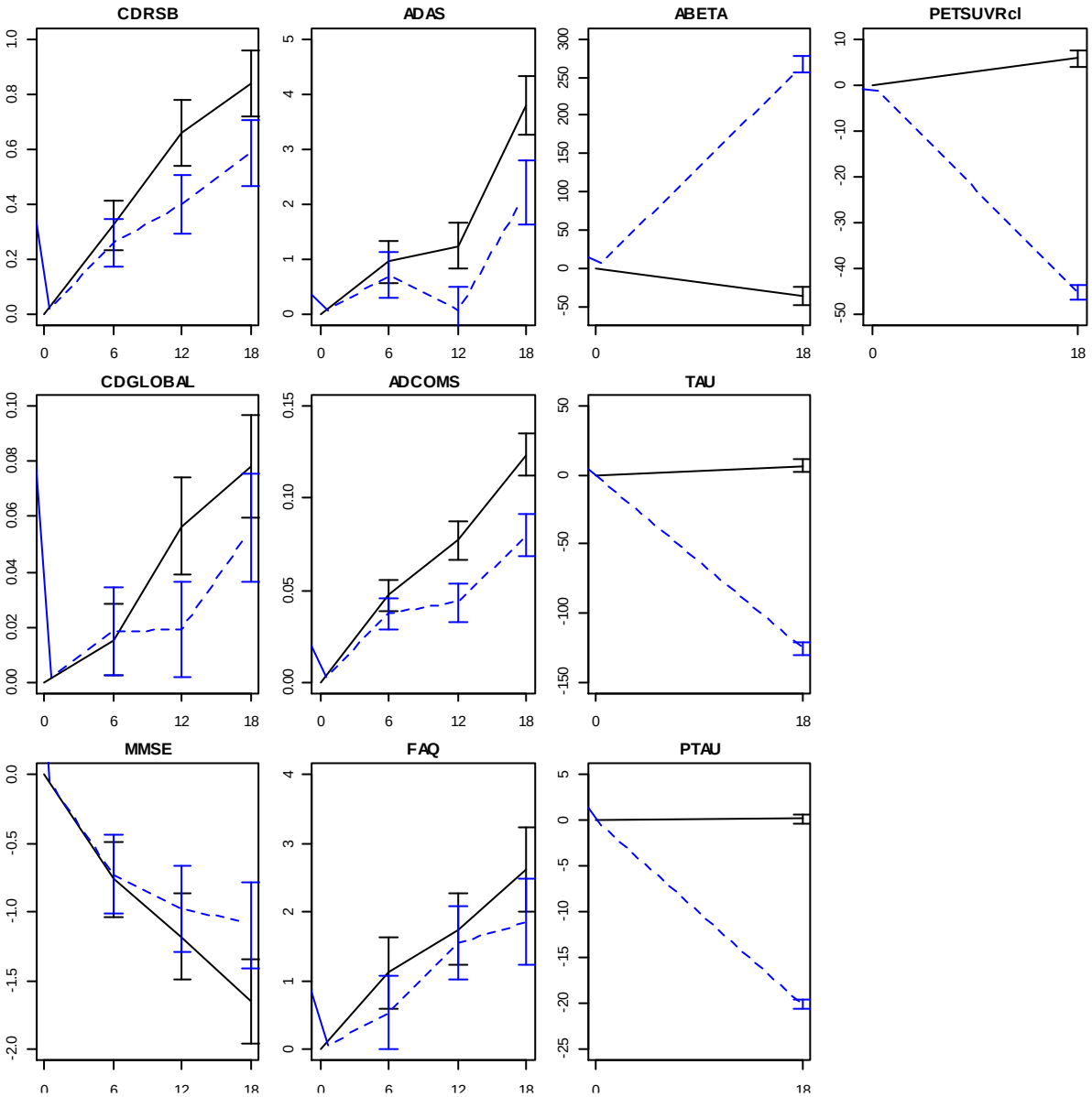

Figure 2: efficacy outcomes: mean change from baseline for control (solid) and intervention (dashed) arm (standard error presented in bars, data labels containing number of observations).

Table 4: Adverse events after 18 months.

	Control (SOC + placebo) n=654		**Intervention (SOC + DMT) n=654**	
	Total	**Symptomatic**	**Total**	**Symptomatic**
ARIA, n (%)	59 (9.0%)	4 (6.7%)	208 (31.8%)	35 (17.0%)
ARIA-E, n (%)	9 (1.4%)	1 (14.3%)	136 (20.8%)	30 (22.1%)
ARIA-H, n (%)	55 (8.4%)	3 (4.8%)	158 (24.2%)	7 (4.1%)
Fall, n (%)	68 (10.4%)	n/a	82 (12.6%)	n/a
Headache, n (%)	93 (14.2%)	n/a	103 (15.8%)	n/a
Infusion reaction, n (%)	22 (3.4%)	n/a	111 (17.0%)	n/a
SAE, n (%)	94 (14.4%)	n/a	99 (15.2%)	n/a
Death, n (%)	5 (0.8%)	n/a	7 (1.0%)	n/a

Abbreviations: ARIA, amyloid-related imaging abnormality; ARIA-E, amyloid-related imaging abnormalities with edema or effusions; ARIA-H, amyloid-related imaging abnormality with hemosiderin deposit; SAE, serious adverse event.

ANALYSIS

Model outcomes (table 1 and 2) will be tabulated and graphed. As there is no established methodology for evaluating concordance in health-economic simulation modelling, between-model differences will be interpreted quantitatively.

RESULTS

REFINEMENT RESEARCH METHODOLOGY

[planned] Refinement was done by 2 scheduled optional meetings and ad-hoc discussion. One group ad-hoc discussed the benchmark scenario suggesting to use extreme scenario as a method to better understand model mechanics. Although a useful option (as showed in …) this fell outside the focus of this workshop.

[planned] During the 2 scheduled optional meetings the following suggestions were made. … This resulted in the following changes to the benchmark scenario.

MODELS USED AND CHANGES MADE AS PART OF THE COMPARISON PROCESS

[planned] Documentation of models used (description, diagram and equation/rate/estimate of MCI dementia conversion, reference to detailed publication/documentation).

[planned] Documentation of changes made to the structure and implementation of key aspect (disease progression, treatment effect, mortality, etc.) as part of the comparison process.

BETWEEN-MODEL VARIABILITY

[planned] Qualitative description of results (referring to result tables). Report range (min/max) and indicate this reflects only between-model variation (not within model variation). Do not report mean outcomes (as their assumptions are not met and this falls outside our study aim).

[planned] Summary tables 5 and 6 containing model outcomes; and graphical representations of them (similar to 2020 workshop).

[planned] Qualitative description of underlying causes for differences and similarities.

[planned] Comment on the quality of the models included where relevant to better understand differences.

Table 5: Template table to report cumulative outcomes over 10-year time horizon (mean per person); if applicable to model type half-cycle correction was applied), separate for male and female.

	Control	Intervention	Difference
Cumulative person-years over 10-year time horizon (mean per person)			
Alive			
MCI			
Mild dementia			
Moderate dementia			
Severe dementia			
Domain-specific[1]:			
Mild cognition			
Moderate cognition			
Severe cognition			
Mild function			
Moderate function			
Severe function			
Mild behavior			
Moderate behavior			
Severe behavior			
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		

[1] suggested cut-offs for MMSE (21-30 = mild, 10-20 = moderate, 0-9 = severe). Feel free to apply mapping (e.g., https://doi-org.mu.idm.oclc.org/10.3233/jad-210060). As modeling group participant you are free to provide any of these outcomes that fit your model best or is possible to translate your model outcomes to (e.g., using mapping).

Table 6: Template table to report proportion of persons in each state over time in the control and intervention strategy over a 25-year time horizon. Proportions at beginning of year (i.e., 0 means day one of the first year, thus no half-cycle correction should be applied), separate for male and female.

Year (control)	MCI	Mild dementia	Moderate dementia	Severe dementia	Death
0	1	0	0	0	0
1					
2					
3					
…					
20					
Year (intervention)	MCI	Mild dementia	Moderate dementia	Severe dementia	Death
0	1	0	0	0	0
1					
2					
3					
…					
20					
Year (difference)	MCI	Mild dementia	Moderate dementia	Severe dementia	Death
0	1	0	0	0	0
1					
2					
3					
…					
20					

REFERENCES

den Boon S, Jit M, Brisson M, Medley G, Beutels P, White R, Flasche S, Hollingsworth TD, Garske T, Pitzer VE, Hoogendoorn M, Geffen O, Clark A, Kim J, Hutubessy R. Guidelines for multi-model comparisons of the impact of infectious disease interventions. BMC Med. 2019 Aug 19;17(1):163. doi: 10.1186/s12916-019-1403-9.

Budd Haeberlein S, Aisen PS, Barkhof F, Chalkias S, Chen T, Cohen S, Dent G, Hansson O, Harrison K, von Hehn C, Iwatsubo T, Mallinckrodt C, Mummery CJ, Muralidharan KK, Nestorov I, Nisenbaum L, Rajagovindan R, Skordos L, Tian Y, van Dyck CH, Vellas B, Wu S, Zhu Y, Sandrock A. Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease. J Prev Alzheimers Dis. 2022;9(2):197-210. doi: 10.14283/jpad.2022.30. PMID: 35542991.

Campbell H, Briggs A, Buxton M, Kim L, Thompson S. The credibility of health economic models for health policy decision-making: The case of population screening for abdominal aortic aneurysm. J Heal Serv Res Policy 2007;12:11–7. doi:10.1258/135581907779497594.

Eddy DM, Hollingworth W, Caro JJ, Tsevat J, McDonald KM, Wong JB. Model transparency and validation: A report of the ISPOR-SMDM modeling good research practices task force-7. Value Heal 2012;15:843–50. doi:10.1016/j.jval.2012.04.012.

Gustavsson A, Green C, Jones RW, Förstl H, Simsek D, de Reydet de Vulpillieres F, et al. Current issues and future research priorities for health economic modelling across the full continuum of Alzheimer's disease. Alzheimer's Dement 2017;13:312–21. doi:10.1016/j.jalz.2016.12.005.

Handels RLH, Green C, Gustavsson A, Herring WL, Winblad B, Wimo A, Sköldunger A, Karlsson A, Anderson R, Belger M, Brück C, Espinosa R, Hlávka JP, Jutkowitz E, Lin PJ, Mendez ML, Mar J, Shewmaker P, Spackman E, Tafazzoli A, Tysinger B, Jönsson L; IPECAD modeling workshop 2020 participants. Cost-effectiveness models for Alzheimer's disease and related dementias: IPECAD modeling workshop cross-comparison challenge. Alzheimers Dement. 2022 Oct 25. doi: 10.1002/alz.12811. Epub ahead of print. PMID: 36284403.

Hernandez L, Ozen A, DosSantos R, Getsios D. Systematic Review of Model-Based Economic Evaluations of Treatments for Alzheimer's Disease. Pharmacoeconomics. 2016 Jul;34(7):681-707. doi: 10.1007/s40273-016-0392-1. PMID: 26899832.

Nguyen KH, Comans TA, Green C. Where are we at with model-based economic evaluations of interventions for dementia? a systematic review and quality assessment. Int Psychogeriatr. 2018 Nov;30(11):1593-1605. doi: 10.1017/S1041610218001291. PMID: 30475198.

Oliver K, Innvar S, Lorenc T, Woodman J, Thomas J. A systematic review of barriers to and facilitators of the use of evidence by policymakers. BMC Health Serv Res 2014;14. doi:10.1186/1472-6963-14-2.

Søgaard R, Lindholt J. Evidence for the credibility of health economic models for health policy decision-making: A systematic literature review of screening for abdominal aortic aneurysms. J Heal Serv Res Policy 2012;17:44–52. doi:10.1258/jhsrp.2011.010133.

Swanson CJ, Zhang Y, Dhadda S, Wang J, Kaplow J, Lai RYK, Lannfelt L, Bradley H, Rabe M, Koyama A, Reyderman L, Berry DA, Berry S, Gordon R, Kramer LD, Cummings JL. A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Aβ protofibril antibody. Alzheimers Res Ther. 2021 Apr 17;13(1):80. doi: 10.1186/s13195-021-00813-8. Erratum in: Alzheimers Res Ther. 2022 May 21;14(1):70. PMID: 33865446; PMCID: PMC8053280.

Vemer P, Corro Ramos I, van Voorn GA, Al MJ, Feenstra TL. AdViSHE: A Validation-Assessment Tool of Health-Economic Models for Decision Makers and Model Users. Pharmacoeconomics. 2016 Apr;34(4):349-61. doi: 10.1007/s40273-015-0327-2. PMID: 26660529; PMCID: PMC4796331.

Possible sources to consider for reflecting a U.S. setting (voluntary basis):

- **Life table**:
    - Arias E, Xu J. United States Life Tables, 2019. National Vital Statistics Reports, Vol. 70, No. 19, March 22, 2022. Retrieved from: https://www.cdc.gov/nchs/data/nvsr/nvsr70/nvsr70-19.pdf
    - Table 1 (male/female together) or table 2 (male) and table 3 (female).
    - Excel version of table 1: https://ftp.cdc.gov/pub/Health_Statistics/NCHS/Publications/NVSR/70-19/Table01.xlsx
    - Excel version of table 2: https://ftp.cdc.gov/pub/Health_Statistics/NCHS/Publications/NVSR/70-19/Table02.xlsx
    - Excel version of table 3: https://ftp.cdc.gov/pub/Health_Statistics/NCHS/Publications/NVSR/70-19/Table03.xlsx
- **Utilities** by AD-dementia severity state in terms of cognition:
    - Questionable, mild, moderate, severe:
        - Neumann PJ, Kuntz KM, Leon J, Araki SS, Hermann RC, Hsu MA, Weinstein MC. Health utilities in Alzheimer's disease: a cross-sectional study of patients and caregivers. Med Care. 1999 Jan;37(1):27-32. doi: 10.1097/00005650-199901000-00005. PMID: 10413389.
        - Table 2
    - MCI and mild, moderate and severe dementia (multi-country, select US):
        - Landeiro F, Mughal S, Walsh K, Nye E, Morton J, Williams H, Ghinai I, Castro Y, Leal J, Roberts N, Wace H, Handels R, Lecomte P, Gustavsson A, Roncancio-Diaz E, Belger M, Jhuti GS, Bouvy JC, Potashman MH, Tockhorn-Heidenreich A, Gray AM; ROADMAP consortium. Health-related quality of life in people with predementia Alzheimer's disease, mild cognitive impairment or dementia measured with preference-based instruments: a systematic literature review. Alzheimers Res Ther. 2020 Nov 18;12(1):154. doi: 10.1186/s13195-020-00723-1. PMID: 33208190; PMCID: PMC7677851.
- **Costs** by AD severity state in terms of cognition:
    - MCI and mild dementia:
        - Robinson RL, Rentz DM, Andrews JS, Zagar A, Kim Y, Bruemmer V, Schwartz RL, Ye W, Fillit HM. Costs of Early Stage Alzheimer's Disease in the United States: Cross-Sectional Analysis of a Prospective

Cohort Study (GERAS-US)1. J Alzheimers Dis. 2020;75(2):437-450. doi: 10.3233/JAD-191212. PMID: 32250304; PMCID: PMC7306889.

- Table 4

- Mild, moderate and severe dementia:
  - Gustavsson A, Brinck P, Bergvall N, Kolasa K, Wimo A, Winblad B, Jönsson L. Predictors of costs of care in Alzheimer's disease: a multinational sample of 1222 patients. Alzheimers Dement. 2011 May;7(3):318-27. doi: 10.1016/j.jalz.2010.09.001. PMID: 21575872.
  - Table 3: country US